Amendment to the Specification

Please delete the existing title and replace therefore:

Nucleic Acids Encoding Tumor Necrosis Factor Receptor TR13

Please amend paragraph **[0001]** as follows:

[0001] This application is a continuation-in-part of, and claims benefit under 35 U.S.C. § 120 to, U.S. Patent Application No. 09/618,570, filed July 14, 2000; which claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Nos. 60/144,087, 60/149,450, 60/149,712, and 60/153,089, which were filed on July 16, 1999, ~~July~~August 18, 1999, August 20, 1999, and September 10, 1999, respectively; and also claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/261,960, filed January 17, 2001, each of which is hereby incorporated by reference in its entirety.

Please amend paragraphs **[0015]** to **[0019]**, **[0021]**, **[0022]**, **[0024]**, **[0025]**, **[0028]** to **[0030]**, **[0032]** to **[0036]**, **[0038]** to **[0041]**, **[0045]**, **[0046]**, **[0049]**, **[0050]**, **[0055]**, **[0056]**, **[0059]**, **[0060]**, **[0063]** to **[0067]**, **[0071]** to **[0074]**, **[0080]**, **[0086]** to **[0089]**, **[0091]** to **[0097]**, **[0100]** to **[0103]**, **[0108]**, **[0111]**, **[0118]**, **[0119]**, **[0121]**, **[0126]**, **[0130]**, **[0131]**, **[0138]** to **[0140]**, **[0143]**, **[0224]**, **[0225]**, **[0228]** to **[0232]**, **[0234]** to **[0237]**, **[0239]**, **[0241]**, **[0243]**, **[0244]**, **[0246]**, **[0247]**, **[0253]**, **[0258]**, **[0259]**, **[0263]**, **[0267]** to **[0270]**, **[0292]**, **[0295]**, **[0297]**, **[0299]**, **[0301]**, **[0302]**, **[0306]**, **[0309]**, **[0318]**, **[0323]**, **[0333]**, **[0334]**, **[0710]**, **[0715]**, **[0723]**, **[0725]**, **[0731]**, **[0732]**, **[0735]**, **[0740]**, **[0794]**, **[0796]**, **[0798]**, **[0800]**, **[0802]**, **[0804]**, **[0814]** to **[0820]**, and **[0840]** as follows, please note that the underlined portions of oligonucleotide sequences in paragraphs **[0794]**,

[0796], **[0798]**, **[0800]**, **[0802]**, **[0804]**, **[0815]** to **[0820]** and **[0840]** are not being amended:

[0015] The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the TR13 receptor having the amino acid sequence shown in SEQ ID NO:2 (Figures 1A-~~C~~D), amino acid sequence shown in SEQ ID NO:40 (Figures 7A-~~D~~E) or the amino acid sequence encoded by the cDNA clone deposited as American Type Culture Collection ("ATCC") Deposit No. PTA-349 (HWLHM70) on July 13, 1999, and/or the amino acid sequence encoded by the cDNA clone deposited as American Type Culture Collection ("ATCC") Deposit No. PTA-507 (HWLHN83) on August 12, 1999. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209. It would be apparent to the skilled artisan that the various methods of use, including but not limited to diagnostic and therapeutic uses described herein, for the TR13 receptor polynucleotides and polypeptides would apply equally to all variants and fragments thereof (e.g., fragments of the TR13 receptor disclosed and described herein in Figures 1A-~~C~~D, Figure 7A-~~D~~E, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:39, SEQ ID NO:40 and/or contained or encoded by one or both of the deposited cDNA clones HWLHM70 and HWLHN83).

[0016] The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them for production of TR13 polypeptides (e.g., the TR13 polypeptide sequence shown in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E, or a fragment thereof) by recombinant techniques.

[0017] The invention further provides an isolated TR13 polypeptide (e.g., the TR13 polypeptide sequence shown in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E or fragments thereof) having an amino acid sequence encoded by a polynucleotide described herein (e.g., the polynucleotide sequence shown in SEQ ID NO:1 and/or SEQ ID NO:39, or a fragment thereof).

[0018] The present invention also provides diagnostic assays such as quantitative and diagnostic assays for detecting levels of TR13 polynucleotide and/or protein (e.g., the TR13 protein shown in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E, or fragments thereof). Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-

expression of TR13, or soluble form thereof, compared to normal control tissue samples may be used to detect the presence of tumors.

[0019] The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the TR14 receptor having the amino acid sequence shown in SEQ ID NO:61 (Figures 10A-H), and/or the amino acid sequence encoded by the cDNA clone deposited as American Type Culture Collection ("ATCC") Deposit No. PTA-348 (HMSHK47) on July 13, 1999. While the sequence of SEQ ID NO:61 and Figures 10A-H are preferred embodiments of TR14 receptor protein, the present invention provides alternative isolated nucleic acid molecule embodiments comprising a polynucleotide encoding the TR14 receptor having the amino acid sequence shown in SEQ ID NO:5 (Figures 4A-~~D~~E). The sequence of amino acid residues T-78 to M-231 of SEQ ID NO:61 is identical to the sequence of amino acid residues T-73 to M-226 of SEQ ID NO:5. It would be apparent to the skilled artisan that the various methods of use, including, but not limited to, diagnostic and therapeutic uses described herein, for the TR13 receptor polynucleotides and polypeptides would apply equally to all variants and fragments thereof (e.g., fragments of the TR14 receptor disclosed and described in Figures 10A-H and SEQ ID NOS:60 and 61, or, alternatively, Figures 4A-~~D~~E and SEQ ID NO:4, SEQ ID NO:5 and/or contained or encoded by the deposited cDNA clone (HMSHK47)).

[0021] The invention further provides an isolated TR14 polypeptide (e.g., the TR14 polypeptide sequence shown in Figures 10A-H or, alternatively, Figures 4A-~~D~~E, or fragments thereof) having an amino acid sequence encoded by a polynucleotide described herein (e.g., the polynucleotide sequence shown in SEQ ID NO:60, or, alternatively SEQ ID NO:4, or fragments thereof).

[0022] The present invention also provides diagnostic assays such as quantitative and diagnostic assays for detecting levels of TR14 polynucleotide and/or protein (e.g., the TR14 polypeptide sequence disclosed in Figures 10A-H or 4A-~~D~~E, or fragments thereof). Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of TR14, or soluble form thereof, compared to normal control tissue samples may be used to detect the presence of tumors.

[0024] Thus, the invention further provides a method for inhibiting TR13 mediated signaling and/or apoptosis induced by a TNF-family ligand, which involves administering to a cell which expresses the TR13 polypeptide (i.e., the TR13 polypeptide shown in

Figures 1A-~~C~~D and/or Figures 7A-~~D~~E, or a fragment thereof) an effective amount of a TR13 antagonist capable of decreasing TR13 mediated apoptosis and/or decreasing TR13 mediated signaling. Preferably, TR13 mediated signaling is decreased to treat a disease wherein increased apoptosis is exhibited.

[0025] Thus, the invention further provides a method for promoting TR13 mediated signalling and/or apoptosis induced by a TNF-family ligand, which involves administering to a cell which expresses the TR13 polypeptide (e.g., the TR13 polypeptide shown in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E, or a fragment thereof) an effective amount of a TR13 agonist capable of increasing TR13 mediated apoptosis and/or increasing TR13 mediated signaling. Preferably, TR13 mediated signaling is increased to treat a disease wherein decreased apoptosis is exhibited.

[0028] In a further aspect, the present invention is directed to a method for enhancing TR13 mediated signaling induced by a TNF-family ligand (e.g., Fas Ligand and/or AIM-II ("LIGHT") (International application publication number WO 97/34911, published September 25, 1997)) which involves administering to a cell which expresses the TR13 polypeptide (e.g., the polypeptide shown in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E, or a fragment thereof) an effective amount of an agonist capable of increasing TR13 mediated activity. Preferably, TR13 mediated activity is increased to treat a disease wherein decreased apoptosis is exhibited.

[0029] Whether any candidate "agonist" or "antagonist" of the present invention can enhance or inhibit TR13 mediated signaling can be determined using art-known TNF-family ligand/receptor cellular response assays, including those described in more detail below. Thus, in a further aspect, a screening method is provided for determining whether a candidate agonist or antagonist is capable of enhancing or inhibiting a cellular response to a TR13 TNF-family ligand. The method involves contacting cells which express the TR13 polypeptide (e.g., the polypeptide shown in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E, or a fragment thereof) with a candidate compound and a TNF-family ligand (e.g., Fas Ligand and/or AIM-II (International application publication number WO 97/34911, published September 25, 1997)), assaying a cellular response, and comparing the cellular response to a standard cellular response, the standard being assayed when contact is made with the ligand in absence of the candidate compound, whereby an increased cellular response over the standard indicates that the candidate compound is an agonist of the

ligand/receptor signaling pathway and a decreased cellular response compared to the standard indicates that the candidate compound is an antagonist of the ligand/receptor signaling pathway. By the invention, a cell expressing a TR13 polypeptide (e.g., the polypeptide shown in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E, or a fragment thereof) can be contacted with either an endogenous or exogenously administered TNF-family ligand.

[0030] In a further aspect, the present invention is directed to a method for enhancing apoptosis TR14 mediated signaling induced by a TNF-family ligand, which involves administering to a cell which expresses the TR14 polypeptide (e.g., the polypeptide shown in Figures 10A-H, or, alternatively 4A-~~D~~E, or a fragment thereof) an effective amount of an agonist capable of increasing TR14 mediated activity. Preferably, TR14 mediated activity is increased to treat a disease wherein decreased apoptosis is exhibited.

[0032] Whether any candidate "agonist" or "antagonist" of the present invention can enhance or inhibit TR14 mediated signaling can be determined using art-known TR14 TNF-family ligand/receptor cellular response assays, including those described in more detail below. Thus, in a further aspect, a screening method is provided for determining whether a candidate agonist or antagonist is capable of enhancing or inhibiting a cellular response to a TNF-family ligand. The method involves contacting cells which express the TR14 polypeptide with a candidate compound and a TNF-family ligand, assaying a cellular response, and comparing the cellular response to a standard cellular response, the standard being assayed when contact is made with the ligand in absence of the candidate compound, whereby an increased cellular response over the standard indicates that the candidate compound is an agonist of the ligand/receptor signaling pathway and a decreased cellular response compared to the standard indicates that the candidate compound is an antagonist of the ligand/receptor signaling pathway. By the invention, a cell expressing the TR14 polypeptide (e.g., the polypeptide shown in Figures 10A-H, or, alternatively 4A-~~D~~E) can be contacted with either an endogenous or exogenously administered TNF-family ligand.

[0033] Figures 1A-~~C~~D shows the nucleotide (SEQ ID NO:1) and deduced amino acid sequence (SEQ ID NO:2) of the TR13 receptor. Predicted amino acids from about 105 to about 170, about 251 to about 265, about 331 to about 410, and about 580 to about 610 constitute the cysteine-rich domains (amino acid residues from about 105 to about 170,

about 251 to about 265, about 331 to about 410, and about 580 to about 610 in SEQ ID NO:2) and are represented by the underlined amino acid regions; amino acids from about 139 to about 142, about 140 to about 143, about 153 to about 156, about 293 to about 296, about 325 to about 328, about 421 to about 424, about 466 to about 469, about 696 to about 699, and about 728 to about 731 constitute potential sites of N-glycosylation (amino acid residues from about 139 to about 142, about 140 to about 143, about 153 to about 156, about 293 to about 296, about 325 to about 328, about 421 to about 424, about 466 to about 469, about 696 to about 699, and about 728 to about 731 in SEQ ID NO:2) which are represented by the bolded amino acids; amino acids from about 312 to about 315, and about 458 to about 461, constitute potential cAMP phosphorylation sites (amino acid residues from about from about 312 to about 315, and about 458 to about 461 in SEQ ID NO:2) and are represented by asterisks (*) above the amino acid residues; amino acids from about 50 to about 53, about 66 to about 69, about 80 to about 83, about 276 to about 279, about 311 to about 314, about 438 to about 441, about 559 to about 562, about 564 to about 567, about 698 to about 701, and about 725 to about 728 constitute potential sites of protein kinase C (PKC) phosphorylation (amino acid residues from about 50 to about 53, about 66 to about 69, about 80 to about 83, about 276 to about 279, about 311 to about 314, about 438 to about 441, about 559 to about 562, about 564 to about 567, about 698 to about 701, and about 725 to about 728 in SEQ ID NO:2) and are represented by the italicized amino acid residues; amino acids from about 80 to about 83, about 89 to about 92, about 180 to about 183, about 198 to about 201, about 214 to about 217, about 272 to about 275, about 306 to about 309, about 510 to about 513, about 529 to about 532, about 584 to about 587, about 609 to about 312, about 642 to about 645, and about 698 to about 701 casein kinase II phosphorylation sites (amino acid residues from about 80 to about 83, about 89 to about 92, about 180 to about 183, about 198 to about 201, about 214 to about 217, about 272 to about 275, about 306 to about 309, about 510 to about 513, about 529 to about 532, about 584 to about 587, about 609 to about 312, about 642 to about 645, and about 698 to about 701 in SEQ ID NO:2) and are represented by the double underlined amino acids; amino acids from about 69 to about 74, about 149 to about 154, about 154 to about 159, about 163 to about 168, about 212 to about 217, about 248 to about 253, about 365 to about 370, about 383 to about 388, about 393 to about 398, about 588 to about 593, about 623 to about 628, about 661 to about 666, and about 665 to about 670 N-

myristoylation sites (amino acids from about 69 to about 74, about 149 to about 154, about 154 to about 159, about 163 to about 168, about 212 to about 217, about 248 to about 253, about 365 to about 370, about 383 to about 388, about 393 to about 398, about 588 to about 593, about 623 to about 628, about 661 to about 666, and about 665 to about 670 in SEQ ID NO:2) and are represented by the strikethrough amino acids (e.g. ~~Q~~); and amino acids from about 456 to about 459 constitute a potential amidylation site (amino acid residues from about 456 to about 459 of SEQ ID NO:5) and is represented by the lowercase amino acids.

[0034] Figures 2A-~~C~~D show the regions of similarity between the amino acid sequences of the TR13 receptor protein (SEQ ID NO:2), and the OX40 protein (SEQ ID NO:3).

[0035] Figure 3 shows an analysis of the TR13 amino acid sequence (SEQ ID NO:2). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues from about M1 to about A9, about K12 to about L20, about N47 to about T55, about H58 to about S66, about D63 to about S71, about P77 to about F85, about A90 to about Q98, about F136 to about Q144, about S152 to about C160, about R159 to about A167, about A211 to about M219, about M235 to about V243, about V266 to about V274, about W277 to about S285, about I290 to about F298, about A310 to about V318, about E343 to about C351, about I360 to about H368, about G391 to about I399, about F409 to about T417, about S436 to about Y444, about C453 to about S461, about I472 to about S480, about Y548 to about S556, about C557 to about I565, about V567 to about V575, about T584 to about G592, about R632 to about G640, about W680 to about Y688, about Q684 to about K692, about T698 to about A706, about S726 to about S734, and about S734 to about L742 of SEQ ID NO:2 (Figures 1A-C) correspond to the highly antigenic regions of the TR13 protein, predicted using the Jameson-Wolf antigenic index (See Figure 3 and Table I). These highly antigenic fragments correspond to the amino acid residues illustrated in Figures 1A-~~C~~D and in SEQ ID NO:2.

[0036] Figures 4A-~~D~~E shows the nucleotide (SEQ ID NO:4) and deduced amino acid sequence (SEQ ID NO:5) of the TR14 receptor. The predicted extracellular domain constitutes amino acids from about 1 to about 133 (amino acid residues from 1 to 133 of

SEQ ID NO:5) and are represented by the underlined amino acids; amino acids from about 65 to about 85 constitute a conserved cysteine-rich domain (amino acid residues from about 65 to about 85 of SEQ ID NO:5) and is represented by the italized amino acid residues; amino acids from about 134 to about 150 constitute the predicted transmembrane domain (amino acid residues from about 134 to about 150 in SEQ ID NO:5) which are represented by the double underlined amino acid residues; amino acid residues from about 151 to about 226 constitutes the predicted intracellular domain (amino acid residues from about 151 to about 226 of SEQ ID NO:5) and are represented by the lower case amino acid residues; amino acids from about 178 to about 180 constitute potential protein kinase C (PKC) phosphorylation sites (amino acid residues from about 178 to about 180 of SEQ ID NO:5) and are represented by asterisks (*) above the amino acid residues; amino acids from about 5 to about 8, about 118 to about 121, about 178 to about 181, and about 193 to about 196 constitute potential sites of casein kinase II phosphorylation (amino acid residues from about 5 to about 8, about 118 to about 121, about 178 to about 181, about 193 to about 196 of SEQ ID NO:5) and are represented by the strikethrough amino acid residues; and amino acids from about 9 to about 14 contitutes a potential N-myristoylation site (amino acid residues from about 9 to about 14 of SEQ ID NO:5) and is represented by the bold amino acids.

[0038] Figure 6 shows an analysis of the TR14 amino acid sequence (SEQ ID NO:5). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues from about T3 to about S11, from about V16 to about R24, from about Q44 to about M52, from about F85 to about G93, from about T103 to about V111, from about F161 to about G169, from about V187 to about A195, from about P218 to about M226 of SEQ ID NO:5 (Figures 4A-~~D~~E) correspond to the highly antigenic regions of the TR14 protein, predicted using the Jameson-Wolf antigenic index (See Figure 6 and Table II). These highly antigenic fragments correspond to the amino acid residues illustrated in Figures 4A-~~D~~E and in SEQ ID NO:5.

[0039] Figures 7A-~~D~~E shows the nucleotide (SEQ ID NO:39) and deduced amino acid sequence (SEQ ID NO:40) of the full-length TR13 receptor. The predicted signal sequence constitutes amino acids from about 1 to about 41 (amino acid residues from

about 1 to about 41 of SEQ ID NO:40) and are represented by the dotted underlined amino acids; amino acids from about 42 to about 906 constitutes the predicted extracellular domain (amino acid residues from 42 to 906 of SEQ ID NO:40) and are represented by the single underlined amino acids; amino acids from about 271 to about 421 and from about 585 to about 595 constitute conserved cysteine-rich domains (amino acid residues from about 271 to about 421 and from about 585 to about 595 of SEQ ID NO:40) and is represented by the italized amino acid residues; amino acids from about 907 to about 931 constitute the predicted transmembrane domain (amino acid residues from about 907 to about 931 in SEQ ID NO:40) which are represented by the double underlined amino acid residues; amino acid residues from about 932 to about 1001 constitutes the predicted intracellular domain (amino acid residues from about 932 to about 1001 of SEQ ID NO:40) and are represented by the lower case amino acid residues; amino acids from about 11 to about 13, about 18 to about 20, 107 to about 109, about 156 to about 158, about 224 to about 226, about 301 to about 303, about 317 to about 319, about 331 to about 333, about 527 to about 529, about 562 to about 564, about 689 to about 691, about 810 to about 812, about 815 to about 817, about 949 to about 951, and about 976 to about 978 constitute potential protein kinase C (PKC) phosphorylation sites (amino acid residues from about 11 to about 13, about 18 to about 20, 107 to about 109, about 156 to about 158, about 224 to about 226, about 301 to about 303, about 317 to about 319, about 331 to about 333, about 527 to about 529, about 562 to about 564, about 689 to about 691, about 810 to about 812, about 815 to about 817, about 949 to about 951, and about 976 to about 978 of SEQ ID NO:40) and are represented by asterisks (*) above the amino acid residues; amino acids from about 42 to about 45, about 59 to about 62, about 81 to about 84, about 146 to about 149, about 282 to about 285, about 331 to about 334, about 340 to about 343, about 431 to about 434, about 449 to about 452, about 465 to about 468, about 523 to about 526, about 557 to about 560, about 761 to about 764, about 780 to about 783, about 780 to about 783, about 835 to about 838, about 860 to about 863, about 893 to about 896, and about 949 to about 952 constitute potential sites of casein kinase II phosphorylation (amino acid residues from about 42 to about 45, about 59 to about 62, about 81 to about 84, about 146 to about 149, about 282 to about 285, about 331 to about 334, about 340 to about 343, about 431 to about 434, about 449 to about 452, about 465 to about 468, about 523 to about 526, about 557 to about 560, about 761 to about 764, about 780 to about 783,

about 780 to about 783, about 835 to about 838, about 860 to about 863, about 893 to about 896, and about 949 to about 952 of SEQ ID NO:40) and are represented by the strikethrough amino acid residues; amino acids from about 77 to about 82, about 88 to about 93, about 152 to about 157, about 268 to about 273, about 288 to about 293, about 320 to about 325, about 400 to about 405, about 414 to about 419, about 463 to about 468, about 599 to about 604, about 616 to about 621, about 634 to about 639, about 644 to about 649, about 839 to about 844, about 874 to about 879, about 912 to about 917, and about 916 to about 921 constitute potential N-myristoylation sites (amino acid residues from about 77 to about 82, about 88 to about 93, about 152 to about 157, about 268 to about 273, about 288 to about 293, about 320 to about 325, about 400 to about 405, about 414 to about 419, about 463 to about 468, about 599 to about 604, about 616 to about 621, about 634 to about 639, about 644 to about 649, about 839 to about 844, about 874 to about 879, about 912 to about 917, and about 916 to about 921 of SEQ ID NO:40) and are represented by a plus sign ("+") above the amino acids; amino acids from about 50 to about 56, and 109 to about 116 constitute potential tyrosine phosphorylation sites (amino acids from about 50 to about 56, and about 109 to about 116 of SEQ ID NO:40) are represented by the double strikethrough amino acids; and amino acids from about 153 to about 156, 390 to about 393, 391 to about 394, about 404 to about 407, about 544 to about 547, about 576 to about 579, about 672 to about 675, about 717 to about 720, about 947 to about 950, and about 979 to about 982 constitute potential N-glycosylation sites (amino acids from about 153 to about 156, 390 to about 393, 391 to about 394, about 404 to about 407, about 544 to about 547, about 576 to about 579, about 672 to about 675, about 717 to about 720, about 947 to about 950, and about 979 to about 982 of SEQ ID NO:40) which are represented by the shaded amino acids.

[0040] Figures 8A-~~B~~D show the regions of similarity between the amino acid sequences of the full-length TR13 receptor protein (SEQ ID NO:40), and the Tumor Necrosis Factor Receptor II homolog (gb|AAB94382.1) (SEQ ID NO: 41).

[0041] Figure 9 shows an analysis of the full-length TR13 amino acid sequence disclosed in Figures 7A-~~D~~E (SEQ ID NO:40). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues from about M1 to about H9, about V14 to about I22, about H47 to about

H55, about C61 to about R69, about L82 to about E90, about D102 to about P110, about K109 to about S117, about F124 to about H132, about M141 to about E149, about S146 to about C154, about S157 to about W165, about F168 to about T176, about N182 to about N190, about Q207 to about A215, about P213 to about M221, about M221 to about E229, about V233 to about V241, about T253 to about V261, about T282 to about S290, about N298 to about T306, about C308 to about Y316, about K315 to about S323, about P328 to about F336, about A341 to about Q349, about F387 to about Q395, about S403 to about C411, about T409 to about P417, about F443 to about N451, about W451 to about Y459, about A462 to about M470, about G478 to about M486, about A487 to about A495, about V517 to about V525, about T527 to about Q535, about I541 to about F549, about A561 to about V569, about E594 to about C602, about I611 to about H619, about G643 to about I650, about P686 to about K694, about C704 to about S712, about R722 to about I730, about E727 to about T735, about P746 to about G754, about D776 to about L784, about Y799 to about S807, about C808 to about I816, about V818 to about V826, about T835 to about G843, about R883 to about G891, about K932 to about K940, about Q935 to about K943, about T949 to about A957, about S977 to about S985, about S981 to about P989, and about N986 to about L994 of SEQ ID NO:40 (Figures 7A-~~D~~E) correspond to the highly antigenic regions of the TR13 protein, predicted using the Jameson-Wolf antigenic index (See Figure 9 and Table III). These highly antigenic fragments correspond to the amino acid residues illustrated in Figures 7A-~~D~~E and in SEQ ID NO:40.

[0045] The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding a TR13 polypeptide having the amino acid sequence shown in Figures 1A-~~C~~D (SEQ ID NO:2) and/or Figures 7A-~~D~~E (SEQ ID NO:40) and/or fragments or variants thereof. The TR13 polypeptide of the present invention shares sequence homology with the human OX40 homologue (Figures 2A-~~C~~D) and the tumor necrosis factor receptor II homolog (Figures 8A-~~B~~D). The nucleotide sequence shown in Figures 1A-~~C~~D (SEQ ID NO:l) was obtained by sequencing a cDNA clone (HWLHM70), which was deposited on July 13, 1999 at the American Type Culture Collection, and given Accession Number PTA-349. The nucleotide sequence shown in Figures 7A-~~D~~E (SEQ ID NO:39) was obtained, in part, by sequencing a cDNA clone (HWLHN83), which was deposited on August 12, 1999 at the American Type Culture Collection, and given Accession Number PTA-507. The deposited clone is inserted in the pSport1 clone (Life

Technologies, Rockville, MD) using the SalI and NotI restriction endonuclease cleavage sites.

[0046] The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding a TR14 polypeptide having the amino acid sequence shown in Figures 10A-H (SEQ ID NO:51), or, alternatively 4A-~~D~~E (SEQ ID NO:5) and/or fragments or variants thereof, which were determined by sequencing a cloned cDNA. The TR14 polypeptide of the present invention shares sequence homology with the Tumor Necrosis Factor Receptor (Figures 5A-B). The nucleotide sequence shown in Figures 10A-H (SEQ ID NO:60) was obtained by sequencing a cDNA clone (HMSHK47), which was deposited on July 13, 1999 at the American Type Culture Collection, and given Accession Number PTA-348. The deposited clone is inserted in the pBluescript clone (Life Technologies, Rockville, MD) using the EcoRI restriction endonuclease cleavage sites. While SEQ ID NO:60 is a preferred sequence for TR14, an alternative TR14 related sequence is shown in Figures 4A-~~D~~E (SEQ ID NO:4).

[0049] The determined TR13 nucleotide sequence of SEQ ID NO:1 contains an open reading frame encoding a protein of about 750 amino acid residues, and a deduced molecular weight of about 82 kDa. The amino acid sequence of the predicted TR13 receptor is shown in SEQ ID NO:2 from amino acid residue about 1 to residue about 750. Of known members of the TNF receptor family, this TR13 polypeptide shares the greatest degree of homology with human OX40 (See Figures 2A-~~C~~D), including significant sequence homology over multiple cysteine rich domains.

[0050] The determined TR13 nucleotide sequence of SEQ ID NO:39 contains an open reading frame encoding a protein of about 1001 amino acid residues, with a predicted signal encompassing amino acids about 1 to about 41, a predicted extracellular domain encompassing amino acids from about 42 to about 906, a transmembrane domain encompassing amino acids from about 907 to about 931, and an intracellular domain encompassing amino acids from about 932 to 1001, of SEQ ID NO:40, and a deduced molecular weight of about 110 kDa. The amino acid sequence of the predicted TR13 receptor is shown in SEQ ID NO:40 from amino acid residue about 1 to residue about 1001. Of known members of the TNF receptor family, this TR13 polypeptide shares the greatest degree of homology with the tumor necrosis factor receptor II homolog (See

Figures 8A-~~B~~D), including significant sequence homology over multiple cysteine rich domains.

[0055] Therefore, the present invention provides a nucleotide sequence encoding the mature form of the TR13 polypeptide having the amino acid sequence encoded by the cDNA clone identified as ATCC Deposit No. PTA-349 (HWLHM70), and/or of the amino acid sequence shown in Figures 1A-~~C~~D (SEQ ID NO:2). By the mature form of TR13 polypeptide having the amino acid sequence encoded by, for example, the cDNA clone identified as ATCC Deposit No. PTA-349 (HWLHM70) is meant, the mature form(s) of the TR13 receptor produced by expression in a mammalian cell (e.g., COS cells, as described below) of the complete open reading frame encoded by the human DNA sequence of the clone contained in the deposited vector. As indicated herein, the mature form of the TR13 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-349 (HWLHM70), may or may not differ from the predicted mature TR13 protein shown in SEQ ID NO:2 (amino acids from about 1 to about 750) depending on the accuracy of the predicted cleavage site based on computer analysis. Polypeptides encoded by the nucleotide sequences are also encompassed by the invention.

[0056] Therefore, the present invention provides a nucleotide sequence encoding the mature form of the TR13 polypeptide having the amino acid sequence encoded by the cDNA clone identified as ATCC Deposit No. PTA-507 (HWLHN83), and/or of the amino acid sequence as shown in Figures 7A-~~D~~E (SEQ ID NO:40). By the mature form of the TR13 polypeptide having the amino acid sequence encoded by, for example, the cDNA clone identified as ATCC Deposit No. PTA-507 (HWLHN83), is meant, the mature form(s) of the TR13 receptor produced by expression in a mammalian cell (e.g., COS cells, as described below) of the complete open reading frame encoded by the human DNA sequence of the clone contained in the deposited vector. As indicated herein, the mature form of the TR13 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-507 (HWLHN83), may or may not differ from the predicted mature TR13 protein shown in SEQ ID NO:40 (amino acids from about 42 to about 1001) depending on the accuracy of the predicted cleavage site based on computer analysis. Polypeptides encoded by these nucleotide sequences are also encompassed by the invention.

[0059] As one of ordinary skill would appreciate, due to the possibilities of sequencing errors, as well as the variability of cleavage sites for leaders in different known proteins, the predicted full-length TR13 polypeptide encoded by the deposited cDNA clones comprises about 1001 amino acids, but may be anywhere in the range of about 700 to about 1200 amino acids. It will further be appreciated that, the domains described herein have been predicted by computer analysis, and accordingly, depending on the analytical criteria used for identifying various functional domains, the exact "address" of, for example, the extracellular domain, intracellular domain, cysteine-rich domains, and transmembrane domain of TR13 may differ slightly (e.g., the address may "shift" by about 1 to about 20 residues, more likely about 1 to about 5 residues). For example, the exact location of the TR13 cysteine-rich domains in Figures 1A-~~C~~D (SEQ ID NO:2) and/or Figures 7A-~~D~~E (SEQ ID NO:40) may vary slightly (e.g., the address may "shift" by about 1 to about 20 residues, more likely about 1 to about 5 residues) depending on the criteria used to define the motifs. In any event, as discussed further below, the invention further provides polypeptides having various residues deleted from the N-terminus and/or C-terminus of the full-length TR13, including polypeptides lacking one or more amino acids from the N-termini of the extracellular domain described herein, which constitute soluble forms of the extracellular domain of the TR13 polypeptides.

[0060] As one of ordinary skill would appreciate, due to the possibilities of sequencing errors, the preferred predicted full-length TR14 polypeptide encoded by the deposited cDNA clone comprises about 231 amino acids as shown in SEQ ID NO:61, but may be anywhere in the range of 175-275 amino acids. In an alternative embodiment, predicted full-length TR14 polypeptide comprises about 226 amino acids, but may be anywhere in the range of 175-275 amino acids, but may be anywhere in the range of about 45 to about 200 amino acids. It will further be appreciated that, the domains described herein have been predicted by computer analysis, and accordingly, that depending on the analytical criteria used for identifying various functional domains, the exact "address" of, for example, the extracellular domain, intracellular domain, cysteine-rich domains, and transmembrane domain of TR14 may differ slightly (e.g., the address may "shift" by about 1 to about 20 residues, more likely about 1 to about 5 residues). For example, the exact location of the TR14 extracellular domain and/or cysteine-rich domains in Figures 10A-H (SEQ ID NO:61) or, alternatively Figures 4A-~~D~~E (SEQ ID NO:5) may vary slightly (e.g.,

the address may "shift" by about 1 to about 20 residues, more likely about 1 to about 5 residues) depending on the criteria used to define the domain. Additionally, in the event the polypeptide sequence of TR14 is longer than the sequence depicted in Figures 10A-H or, alternatively Figures 4A-~~D~~E, the skilled artisan would appreciate that the sequence could affect the ultimate location of the extracellular, transmembrane, or intracellular domain. In any event, as discussed further below, the invention further provides polypeptides having various residues deleted from the N-terminus and/or C-terminus of the full-length TR14, including polypeptides lacking one or more amino acids from the N-termini of the extracellular domain described herein, which constitute soluble forms of the extracellular domain of the TR14 polypeptides.

[0063] Isolated nucleic acid molecules of the present invention include, for example, DNA molecules comprising, or alternatively consisting of, an open reading frame (ORF) shown in Figures 1A-~~C~~D (SEQ ID NO:1), Figures 7A-~~D~~E (SEQ ID NO:39) and/or contained in a deposited cDNA clone (e.g., HWLHM70 and HWLHN83); DNA molecules comprising, or alternatively consisting of, the coding sequence for the mature TR13 protein shown in Figures 1A-~~C~~D (SEQ ID NO:1) and/or Figures 7A-~~D~~E (SEQ ID NO:39) and/or contained in a deposited cDNA clone (e.g., HWLHM70 and HWLHN83); DNA molecules comprising, or alternatively consisting of, a fragment of the coding sequence for the full-length TR13 protein disclosed in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E and/or encoded by a deposited cDNA clone; and DNA molecules which comprise, or alternatively consist of, a sequence substantially different from those described above, but which, due to the degeneracy of the genetic code, still encode TR13 polypeptides (including fragments of variants thereof). Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate variants.

[0064] Isolated nucleic acid molecules of the present invention include, for example, DNA molecules comprising, or alternatively consisting of, an open reading frame (ORF) shown preferably in Figures 10A-H (SEQ ID NO:60) or, alternatively, in Figures 4A-~~D~~E (SEQ ID NO:4) and/or contained in the deposited cDNA clone (HMSHK47); DNA molecules comprising, or alternatively consisting of, the coding sequence for the mature TR14 protein shown preferably in Figures 10A-H (amino acids 1-164 of SEQ ID NO:61), or alternatively, in Figures ~~7~~4A-~~D~~E (SEQ ID NO:4) and/or

contained in the deposited cDNA clone (HMSHK47); DNA molecules comprising, or alternatively consisting of, a fragment of the coding sequence for the full-length TR14 protein disclosed in preferably in Figures 10A-H or, alternatively, in Figures 4A-~~D~~E and/or encoded by the deposited cDNA clone (HMSHK47); and DNA molecules which comprise a sequence substantially different from those described above, but which, due to the degeneracy of the genetic code, still encode TR14 polypeptides (including fragments or variants thereof). Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate variants.

[0065] In another aspect, the invention provides isolated nucleic acid molecules encoding the TR13 polypeptide having an amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-349 (HWLHM70). In a further embodiment, nucleic acid molecules are provided that encode the mature form of the TR13 polypeptide disclosed in Figures 1A-~~C~~D and/or encoded by the cDNA contained in ATCC Deposit No. PTA-349. In a further embodiment, nucleic acids are provided that the full-length TR13 polypeptide disclosed in Figures 1A-~~C~~D and/or encoded by the deposited cDNA clone, but lacking the N-terminal methionine. In a further embodiment, nucleic acid molecules are provided that encode The invention further provides an isolated nucleic acid molecule having the nucleotide sequence shown in SEQ ID NO:1 or the nucleotide sequence of the TR13 cDNA contained in the above-described deposited cDNA clone, or a nucleic acid molecule having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful, for example, as probes for gene mapping by *in situ* hybridization with chromosomes, and for detecting expression of the TR13 gene in human tissue, for instance, by Northern blot analysis.

[0066] In another aspect, the invention provides isolated nucleic acid molecules encoding the TR13 polypeptide having an amino acid sequence as encoded by the cDNA clone contained in ATCC Deposit No. PTA-507 (HWLHN83). In a further embodiment, nucleic acid molecules are provided that encode the mature form of the TR13 polypeptide disclosed in Figures 7A-~~D~~E, and/or encoded by the cDNA contained in ATCC Deposit No. PTA-507. In a further embodiment, nucleic acid molecules are provided that encode the full-length TR13 polypeptide disclosed in Figures 7A-~~D~~E, and/or encoded by the deposited cDNA clone, but lacking the N-terminal methionine. The invention further provides an isolated nucleic acid molecule having the nucleotide sequence shown in SEQ

ID NO:39 or the nucleotide sequence of the TR13 cDNA contained in the above-described deposited cDNA clone, or a nucleic acid molecule having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful, for example, as probes for gene mapping by *in situ* hybridization with chromosomes, and for detecting expression of the TR13 gene in human tissue, for instance, by Northern blot analysis.

[0067] In another aspect, the invention provides isolated nucleic acid molecules encoding the TR14 polypeptide having an amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-348 (HMSHK47). In a further embodiment, nucleic acid molecules are provided that encode the full-length TR14 polypeptide disclosed in Figures 10A-H or, alternatively, in Figures 4A-~~D~~E, and/or encoded by the deposited cDNA clone, but lacking the N-terminal methionine. The invention further provides an isolated nucleic acid molecule having the nucleotide sequence shown preferably in SEQ ID NO:60 or, alternatively, in SEQ ID NO:4 or the nucleotide sequence of the TR14 cDNA contained in the above-described deposited cDNA clone, or a nucleic acid molecule having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful, for example, as probes for gene mapping by *in situ* hybridization with chromosomes, and for detecting expression of the TR14 gene in human tissue, for instance, by Northern blot analysis.

[0071] The present invention is further directed to fragments of the isolated TR13 nucleic acid molecules described herein. By a fragment of an isolated DNA molecule having the nucleotide sequence of a deposited cDNA clone (e.g., HWLHN83 and/or HWLHM70), or the nucleotide sequence shown in Figures 1A-~~C~~D (SEQ ID NO:1) and/or Figures 7A-~~D~~E (SEQ ID NO:39), or the complementary strand thereto, is intended DNA fragments at least about 15nt, and more preferably at least about 20 nt, or at least 25 nt, still more preferably at least about 30 nt, or at least 35 nt, and even more preferably, at least about 40 nt, or at least about 50 nt in length which are useful, for example, as diagnostic probes and primers as discussed herein. Of course, larger fragments 50-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of the deposited cDNA or as shown in SEQ ID NO:1 and/or SEQ ID NO:39. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the

nucleotide sequence of a deposited cDNA clone or the nucleotide sequence as shown in Figures 1A-~~C~~D (SEQ ID NO:1) and/or Figures 7A-~~D~~E (SEQ ID NO:39). In this context "about" includes the particularly recited size, or may be larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

[0072] The present invention is further directed to fragments of the isolated TR14 nucleic acid molecules described herein. By a fragment of an isolated DNA molecule having the nucleotide sequence of the deposited cDNA clone (HMSHK47), or the nucleotide sequence shown preferably in Figures 10A-H (SEQ ID NO:60) or, alternatively in Figures 4A-~~D~~E (SEQ ID NO:4), or the complementary strand thereto, is intended DNA fragments at least about 15nt, and more preferably at least about 20 nt, or at least 25 nt, still more preferably at least about 30 nt, or at least 35 nt, and even more preferably, at least about 40 nt, or at least 50 nt, in length which are useful, for example, as diagnostic probes and primers as discussed herein. Of course, larger fragments 50-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of the deposited cDNA or as shown preferably in Figures 10A-H (SEQ ID NO:60) or, alternatively in Figures 4A-~~D~~E (SEQ ID NO:4). By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of the deposited cDNA or the nucleotide sequence as shown in preferably in SEQ ID NO:60, or, alternatively, in SEQ ID NO:4. In this context "about" includes the particularly recited size, or may be larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

[0073] Representative examples of TR13 polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 108, from about 109 to about 159, from about 160 to about 210, from about 211 to about 261, from about 262 to about 273, from about 274 to about 324, from about 325 to about 375, from about 376 to about 426, from about 427 to about 477, from about 478 to about 528, from about 529 to about 579, from about 580 to about 630, from about 631 to about 681, from about 682 to about 732, from about 733 to about 744, from about 745 to about 798, from about 799 to about 849, from about 850 to about 900, from about 901 to about 951, from about 952 to about 1002, from about 1003 to about 1053, from about 1054 to about 1104, from about 1105 to about 1155, from about 1156 to about 1164, from about 1165 to about 1197, from

about 1198 to about 1248, from about 1249 to about 1266, from about 1267 to about 1317, from about 1318 to about 1368, from about 1369 to about 1419, from about 1420 to about 1470, from about 1471 to about 1521, from about 1522 to about 1572, from about 1573 to about 1623, from about 1624 to about 1674, from about 1675 to about 1725, from about 1726 to about 1776, from about 1777 to about 1827, from about 1828 to about 1878, from about 1879 to about 1929, from about 1930 to about 1980, from about 1981 to about 2031, from about 2032 to about 2082, from about 2083 to about 2133, from about 2134 to about 2184, from about 2185 to about 2235, from about 2236 to about 2286, from about 2287 to about 2337, from about 2338 to about 2388, from about 2389 to about 2489, from about 2490 to about 2540, from about 2451 to about 2501, from about 2502 to about 2554 of the polynucleotide sequence shown in Figures 1A-~~C~~D (SEQ ID NO:1), or the complementary strand thereto, or the cDNA contained in the deposited clone (HWLHM70). Other representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively consist of, a sequence from about nucleotide 1 to about 362, from about 705 to about 830, from about 31 to about 2280, from about 343 to 414, from about 415 to about 459, from about 460 to about 540, 343 to about 540, from about 781 to about 804, from about 805 to about 830, from about 781 to about 822, from about 1021 to about 1260, from about 1768 to about 1812, from about 1813 to about 1866, from about 1768 to about 1866, from about 31 to about 540, from about 660 to about 984, from about 1057 to about 1470, from about 1672 to about 1806, and/or from about 1924 to about 2256 of the polynucleotide sequence shown in Figures 1A-~~C~~D (SEQ ID NO:1), or the complementary strand thereto. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Polynucleotides which hybridize to any 1, 2, 3, 4, 5 or more of these polynucleotide fragments are also encompassed by the invention. Moreover, polypeptides encoded by these polynucleotides and/or polynucleotide fragments are also encompassed by the invention.

[0074] Additional representative examples of TR13 polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 108, from about 109 to about 159, from about 160 to about 210, from about 211 to about 261, from about 262 to about 273, from about 274 to about 324, from about 325 to about 375, from about 376

to about 426, from about 427 to about 477, from about 478 to about 528, from about 529 to about 579, from about 580 to about 630, from about 631 to about 681, from about 682 to about 732, from about 733 to about 744, from about 745 to about 798, from about 799 to about 849, from about 850 to about 900, from about 901 to about 951, from about 952 to about 1002, from about 1003 to about 1053, from about 1054 to about 1104, from about 1105 to about 1155, from about 1156 to about 1164, from about 1165 to about 1197, from about 1198 to about 1248, from about 1249 to about 1266, from about 1267 to about 1317, from about 1318 to about 1368, from about 1369 to about 1419, from about 1420 to about 1470, from about 1471 to about 1521, from about 1522 to about 1572, from about 1573 to about 1623, from about 1624 to about 1674, from about 1675 to about 1725, from about 1726 to about 1776, from about 1777 to about 1827, from about 1828 to about 1878, from about 1879 to about 1929, from about 1930 to about 1980, from about 1981 to about 2031, from about 2032 to about 2082, from about 2083 to about 2133, from about 2134 to about 2184, from about 2185 to about 2235, from about 2236 to about 2286, from about 2287 to about 2337, from about 2338 to about 2388, from about 2389 to about 2489, from about 2490 to about 2540, from about 2451 to about 2501, from about 2502 to about 2554, about 2600 to about 2650, about 2651 to about 2700, about 2701 to about 2750, about 2751 to about 2800, about 2801 to about 2850, about 2851 to about 2900, about 2901 to about 2950, about 2951 to about 3000, about 3001 to about 3050, about 3051 to about 3100, about 3101 to about 3150, about 3151 to about 3200, about 3201 to about 3250, about 3251 to about 3300, and about 3301 to about 3334 of the polynucleotide sequence shown in Figures 7A-~~D~~E (SEQ ID NO:39), or the complementary strand thereto, or the cDNA contained in the deposited clone (HWLHN83). Other representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively consist of, a sequence from about nucleotide 1 to about 42, from about 181 to about 2775, from about 984 to about 1142, from about 1485 to about 1610, from about 2361 to about 2718, from about 61 to about 3060, from about 58 to about 3060, from about 58 to about 183, from about 58 to about 2775, from about 2776 to about 2850, from about 2851 to about 3060, from about 868 to about 1320, from about 868 to about 915, from about 925 to about 957, about 960 to about 1017, about 1042 to about 1140, about 1267 to about 1320, about 870 to about 1320, about 1810 to about 1842, about 2038 to about 2079, about 2185 to about 2289, about 2995 to about 3054, about 190 to about 237,

about 418 to about 462, about 58 to about 843, about 847 to about 1326, about 1366 to about 2424, about 1812 to about 1842, about 2776 to about 2850, about 2428 to about 3060, about 2851 to about 3060, and/or from about 490 to about 537 of the polynucleotide sequence shown in Figures 7A-~~D~~E (SEQ ID NO:39), or the complementary strand thereto. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Polynucleotides which hybridize to any 1, 2, 3, 4, 5 or more of these polynucleotide fragments are also encompassed by the invention. Moreover, polypeptides encoded by these polynucleotides and/or polynucleotide fragments are also encompassed by the invention. Moreover, polypeptides encoded by the polynucleotides and/or polynucleotide fragments are also encompassed by the invention.

[0080] Alternative representative examples of TR14 polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 108, from about 109 to about 159, from about 160 to about 210, from about 211 to about 261, from about 262 to about 273, from about 274 to about 324, from about 325 to about 375, from about 376 to about 426, from about 427 to about 477, from about 478 to about 528, from about 529 to about 579, from about 580 to about 630, from about 631 to about 681, from about 682 to about 732, from about 733 to about 744, from about 745 to about 798, from about 799 to about 849, from about 850 to about 900, from about 901 to about 951, from about 952 to about 1002, from about 1003 to about 1053, from about 1054 to about 1104, from about 1105 to about 1155, from about 1156 to about 1164, from about 1165 to about 1197, from about 1198 to about 1248, from about 1249 to about 1266, from about 1267 to about 1317, from about 1318 to about 1368, from about 1369 to about 1419, from about 1420 to about 1470, from about 1471 to about 1521, from about 1522 to about 1572, from about 1573 to about 1623, from about 1624 to about 1674, from about 1675 to about 1725, from about 1726 to about 1776, from about 1777 to about 1827, from about 1828 to about 1878, from about 1879 to about 1929, from about 1930 to about 1980, from about 1981 to about 2031, from about 2032 to about 2082, from about 2083 to about 2133, from about 2134 to about 2184, from about 2185 to about 2235, from about 2236 to about 2286, from about 2287 to about 2337, from about 2338 to about 2388, from about 2389 to about 2489, from about 2490 to about 2540, from about 2451 to about 2501, from about 2502 to about 2552, from

about 2553 to about 2603, from about 2604 to about 2654, from about 2655 to about 2705, from about 2706 to about 2756, from about 2806 to about 2856, from about 2857 to about 2907, from about 2908 to about 2958, from about 2959 to about 3009, from about 3010 to about 3060, from about 3061 to about 3111, from about 3112 to about 3162, from about 3163 to about 3213, from about 3214 to about 3264, from about 3265 to about 3315, from about 3316 to about 3366, from about 3367 to about 3417, from about 3418 to about 3468, from about 3469 to about 3519, from about 3520 to about 3566, from about 3567 to about 3599, from about 3600 to about 3649, from about 3650 to about 3699, from about 3700 to about 3749, from about 3750 to about 3799, and/or from 3800 to about 3861 of the polynucleotide sequence shown in Figures 4A-~~D~~E (SEQ ID NO:4), or the complementary strand thereto, or the cDNA contained in the deposited clone (HMSHK47). Other representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 1451, from about 1761 to about 2251, from about 3133 to about 3861, from about 89 to about 766, from about 89 to about 487, from about 488 to about 538, from about 539 to about 766, from about 92 to about 160, from about 212 to about 243, from about 281 to about 313, from about 314 to about 343, from about 281 to about 343, from about 325 to about 433, and/or 550 to about 766 of the polynucleotide sequence shown in Figures 4A-~~D~~E (SEQ ID NO:4), or the complementary strand thereto. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Polynucleotides which hybridize to any 1, 2, 3, 4, 5 or more of these polynucleotide fragments are also encompassed by the invention. Moreover, polypeptides encoded by these polynucleotides and/or polynucleotide fragments are also encompassed by the invention.

[0086] Preferred nucleic acid fragments of the present invention include nucleic acid molecules encoding a member selected from the group: a polypeptide comprising or alternatively, consisting of any combination of one, two, three or all four TR13 cysteine rich domains (amino acid residues from about 105 to about 170, from about 251 to about 264, from about 331 to about 410 and from about 580 to about 610 in Figures 1A-~~C~~D (amino acids from about 105 to about 170, from about 251 to about 265, from about 331 to about 410 and from about 580 to about 610 in SEQ ID NO:1). Since, as discussed above, the location of these domains have been predicted by computer analysis, one of ordinary

skill would appreciate that the amino acid residues constituting these domains may be the particularly recited ranges for each domain or may vary slightly (e.g., by about 1, 2, 3, 4, 5, 10, or 15 residues at either extreme or at both extremes) depending on the criteria used to define each domain.

[0087] Additional preferred nucleic acid fragments of the present invention include nucleic acid molecules encoding a member selected from the group: a polypeptide comprising or alternatively, consisting of the TR13 receptor extracellular domain (amino acids 1 to 906 in Figures 7A-~~D~~E); a polypeptide comprising or alternatively, consisting of, the mature TR13 receptor extracellular domain (amino acids 42 to 906 in Figures 7A-~~D~~E); a polypeptide comprising or alternatively, consisting of, one or more of the TR13 cysteine rich domains disclosed in Figures 7A-~~D~~E (e.g., amino acid residues from about 271 to about 421, from about 271 to about 286, about 290 to about 300, about 301 to about 320, about 329 to about 361, about 404 to about 421, and from about 585 to about 595 in Figures 7A-~~D~~E (amino acid residues from about 271 to about 421, from about 271 to about 286, about 290 to about 300, about 301 to about 320, about 329 to about 361, about 404 to about 421, and from about 585 to about 595 in SEQ ID NO:39 and SEQ ID NO:40); a polypeptide comprising, or alternatively, consisting of the TR13 transmembrane domain (amino acids 907 to 931 in Figures 7A-~~D~~E); and a polypeptide comprising, or alternatively consisting of the TR13 intracellular domain (amino acid 932 to 1001 in Figures 7A-~~D~~E). As above, since the location of these domains have been predicted by computer analysis, one of ordinary skill would appreciate that the amino acid residues constituting these domains may be the particularly recited ranges for each domain or may vary slightly (e.g., by about 1, 2, 3, 4, 5, 10, or 15 residues at either extreme or at both extremes) depending on the criteria used to define each domain.

[0088] It is believed that the cysteine rich motifs of TR13 disclosed in Figures 1A-~~C~~D are important for interactions between TR13 and its ligands. Accordingly, specific embodiments of the invention are directed to polynucleotides encoding polypeptides which comprise, or alternatively consist of, the amino acid sequence of amino acid residues from about 105 to about 170, from about 251 to about 265, from about 331 to about 410, and from about 580 to about 610 of SEQ ID NO:5 (corresponding to amino acid residues from about 105 to about 170, from about 251 to about 265, from about 331 to about 410, and from abour 580 to about 610 of Figures 4A-~~D~~E). In a specific

embodiment, the polynucleotides encoding TR13 polypeptides of the invention comprise or alternatively consist of, polynucleotide sequences encoding any combination of 2, 3, or all four of the cysteine-rich motifs of TR13. In this context, "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

[0089] Further, specific embodiments of the invention are directed to polynucleotides encoding polypeptides which comprise, or alternatively consist of, the amino acid sequence of amino acid residues from about 271 to about 421, from about 271 to about 286, from about 290 to about 300, from about 301 to about 320, about 329 to about 361, about 404 to about 421, and about 585 to about 595 of SEQ ID NO:40 (corresponding to amino acid residues from about 271 to about 421, from about 271 to about 286, from about 290 to about 300, from about 301 to about 320, about 329 to about 361, about 404 to about 421, and about 585 to about 595 of Figures 7A-~~D~~E). In a specific embodiment, the polynucleotides encoding TR13 polypeptides of the invention comprise or alternatively consist of, polynucleotide sequences encoding any combination of 2, 3, or all four of the cysteine-rich motifs of TR13 disclosed in Figures 7A-~~D~~E. In this context, "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

[0091] Preferred nucleic acid fragments of the invention encode a full-length TR13 polypeptide lacking the nucleotides encoding the amino terminal methionine (e.g., nucleotides 61-1001 in Figures 7A-~~D~~E and SEQ ID NO:39), as it is known that the methionine is cleaved naturally and such sequences may be useful in genetically engineering TR13 expression vectors. Polypeptides encoded by such nucleic acids are also contemplated by the invention.

[0092] Preferred nucleic acid fragments of the present invention further include nucleic acid molecules encoding epitope-bearing portions of the TR13 receptor protein. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a polypeptide comprising or alternatively consisting of, amino acid residues from about 1 to about 170 in Figures 1A-~~C~~D (corresponding to about amino acid 1 to about 170 in SEQ ID NO:2); a polypeptide comprising or alternatively consisting of,

amino acid residues from about 210 to about 318 in Figures 1A-~~C~~D (corresponding to about amino acid 210 to about 318 in SEQ ID NO:2); a polypeptide comprising or alternatively consisting of, amino acid residues from about 343 to about 480 in Figures 1A-~~C~~D (corresponding to about amino acid 343 to about 480 in SEQ ID NO:2); a polypeptide comprising or alternatively consisting of, amino acid residues from about 548 to about 592 in Figures 1A-~~C~~D (corresponding to about amino acid 548 to about 592 in SEQ ID NO:2); and a polypeptide comprising or alternatively consisting of, amino acid residues from about 632 to about 742 in Figures 1A-~~C~~D (corresponding to about amino acid 632 to about 742 in SEQ ID NO:2). The inventors have determined that the above polypeptide fragments are antigenic regions of the TR13 protein. Methods for determining other such epitope-bearing portions of the TR13 protein are described in detail below.

[0093] Preferred nucleic acid fragments of the present invention further include nucleic acid molecules encoding antigenic fragments of the TR13 receptor protein. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a polypeptide comprising or alternatively consisting of, amino acid residues from about M1 to about A9, about K12 to about L20, about N47 to about T55, about H58 to about S66, about D63 to about S71, about P77 to about F85, about A90 to about Q98, about F136 to about Q144, about S152 to about C160, about R159 to about A167, about A211 to about M219, about M235 to about V243, about V266 to about V274, about W277 to about S285, about I290 to about F298, about A310 to about V318, about E343 to about C351, about I360 to about H368, about G391 to about I399, about F409 to about T417, about S436 to about Y444, about C453 to about S461, about I472 to about S480, about Y548 to about S556, about C557 to about I565, about V567 to about V575, about T584 to about G592, about R632 to about G640, about W680 to about Y688, about Q684 to about K692, about T698 to about A706, about S726 to about S734, and about S734 to about L742 of SEQ ID NO:2 (Figures 1A-~~C~~D) correspond to the highly antigenic regions of the TR13 protein, predicted using the Jameson-Wolf antigenic index (See Figure 3 and Table I). These highly antigenic fragments correspond to the amino acid residues illustrated in Figure 1A-~~C~~D and in SEQ ID NO:2. In this context, "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1)

nucleotides, at either terminus or at both termini. Methods for determining other such antigenic fragments of the TR13 protein are described in detail below.

[0094] Additional preferred nucleic acid fragments of the present invention further include nucleic acid fragments encoding: a polypeptide comprising or alternatively consisting of, amino acid residues from about 1 to about 262 in Figures 7A-~~D~~E (corresponding to about amino acid 1 to about 262 in SEQ ID NO:40); a polypeptide comprising or alternatively consisting of, amino acid residues from about 264 to about 423 in Figures 7A-~~D~~E (corresponding to about amino acid 264 to about 423 in SEQ ID NO:40); a polypeptide comprising or alternatively consisting of, amino acid residues from about 437 to about 789 in Figures 7A-~~D~~E (corresponding to about amino acid 437 to about 789 in SEQ ID NO:40); and a polypeptide comprising or alternatively consisting of, amino acid residues from about 791 to about 1001 in Figures 7A-~~D~~E (corresponding to about amino acid 791 to about 1001 in SEQ ID NO:40). The inventors have determined that the above polypeptide fragments are antigenic regions of the TR13 protein. Methods for determining other such epitope-bearing portions of the TR13 protein are described in detail below.

[0095] Additional preferred nucleic acid fragments of the present invention encoding antigenic fragments of the TR13 receptor protein include nucleic acid molecules encoding: a polypeptide comprising or alternatively consisting of, amino acid residues from about M1 to about H9, about V14 to about I22, about H47 to about H55, about C61 to about R69, about L82 to about E90, about D102 to about P110, about K109 to about S117, about F124 to about H132, about M141 to about E149, about S146 to about C154, about S157 to about W165, about F168 to about T176, about N182 to about N190, about Q207 to about A215, about P213 to about M221, about M221 to about E229, about V233 to about V241, about T253 to about V261, about T282 to about S290, about N298 to about T306, about C308 to about Y316, about K315 to about S323, about P328 to about F336, about A341 to about Q349, about F387 to about Q395, about S403 to about C411, about T409 to about P417, about F443 to about N451, about W451 to about Y459, about A462 to about M470, about G478 to about M486, about A487 to about A495, about V517 to about V525, about T527 to about Q535, about I541 to about F549, about A561 to about V569, about E594 to about C602, about I611 to about H619, about G643 to about I650, about P686 to about K694, about C704 to about S712, about R722 to about I730, about

E727 to about T735, about P746 to about G754, about D776 to about L784, about Y799 to about S807, about C808 to about I816, about V818 to about V826, about T835 to about G843, about R883 to about G891, about K932 to about K940, about Q935 to about K943, about T949 to about A957, about S977 to about S985, about S981 to about P989, and about N986 to about L994 of SEQ ID NO:40 (Figures 7A-~~D~~E) correspond to the highly antigenic regions of the TR13 protein, predicted using the Jameson-Wolf antigenic index (See Figure 9 and Table III). These highly antigenic fragments correspond to the amino acid residues illustrated in Figure 7A-~~D~~E and in SEQ ID NO:40. In this context, "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Methods for determining other such antigenic fragments of the TR13 protein are described in detail below.

[0096] Additionally, it is believed that the extracellular cysteine rich motif of TR14 disclosed in Figures 10A-H or, alternatively, Figures 4A-~~D~~E is important for interactions between TR14 and its ligands. Accordingly, specific embodiments of the invention are directed to nucleic acid molecules encoding polypeptides which comprise, or alternatively consist of, preferably amino acids Cys-31 to Cys-104 of Figures 10A-B and SEQ ID NO:61, or, alternatively, the amino acid sequence of amino acid residues from about 70 to about 90 of Figure 10A and SEQ ID NO:61 (corresponding to amino acid residues from about 65 to about 85 of Figures 4A-~~D~~E or SEQ ID NO:5). In this context, "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

[0097] Preferred nucleic acid fragments of the present invention include nucleic acid molecules encoding a member selected from the group: a polypeptide comprising or alternatively, consisting of, the TR14 receptor extracellular domain (preferably amino acid residues from about 1 to 138 in Figures 10A-H or, alternatively, from about 1 to about 133 in Figures 4A-~~D~~E); a polypeptide comprising or alternatively, consisting of, the TR14 cysteine rich domain (preferably amino acid residues from about 31 to about 104 of Figures 10A-H, or amino acid residues from about 70 to 90 in Figures 10A, or, alternatively, from about 65 to about 85 in Figures 4A-~~D~~E); a polypeptide comprising or alternatively, consisting of the TR14 transmembrane domain (preferably amino acid residues from about 139 to 155 in Figures 10A-H or, alternatively, 134 to about 150 in

Figures 4A-~~D~~E); and a polypeptide comprising or alternatively, consisting of, the TR14 intracellular domain (preferably amino acid residues from about 156 to about 231 in Figures 10A-H or, alternatively, amino acid residues from about 151 to about 226 in Figures 4A-~~D~~E). Since the location of these domains have been predicted by computer analysis, one of ordinary skill would appreciate that the amino acid residues constituting these domains may be the particularly recited ranges for each domain or may vary slightly (e.g., by about 1, 2, 3, 4, 5, 10, or 15 residues at either extreme or at both extremes) depending on the criteria used to define each domain.

[0100] Alternatively, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a polypeptide comprising or alternatively consisting of, amino acid residues from about 2 to about 24 in Figures 4A-~~D~~E (corresponding to about amino acid 2 to about 24 in SEQ ID NO:5); a polypeptide comprising or alternatively consisting of, amino acid residues from about 42 to about 52 in Figures 4A-~~D~~E (corresponding to about amino acid 42 to about 52 in SEQ ID NO:5); a polypeptide comprising or alternatively consisting of, amino acid residues from about 80 to about 115 in Figures 4A-~~D~~E (corresponding to about amino acid 80 to about 115 in SEQ ID NO:5 and about amino acid 85 to about 120 of SEQ ID NO:61); and a polypeptide comprising or alternatively consisting of, amino acid residues from about 155 to about 226 in Figures 4A-~~D~~E (corresponding to about amino acid 155 to about 226 in SEQ ID NO:5 and about amino acid 160 to about amino acid 231 of SEQ ID NO:61). The inventors have determined that the above polypeptide fragments are antigenic regions of the TR14 protein. Methods for determining other such epitope-bearing portions of the TR14 protein are described in detail below.

[0101] Alternative nucleic acid fragments of the present invention further include nucleic acid molecules encoding antigenic fragments of the TR14 receptor protein. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a polypeptide comprising or alternatively consisting of, amino acid residues of SEQ ID NO:5 (Figures 4A-~~D~~E) from about T3 to about S11, from about V16 to about R24, from about Q44 to about M52, from about F85 to about G93 (about F90 to about G98 of SEQ ID NO:61), from about T103 to about V111 (about T108 to about V116 of SEQ ID NO:61), from about F161 to about G169 (about F165 to about G174 of SEQ ID NO:61), from about V187 to about A195 (from about V192 to about A200 of SEQ ID

NO:61), from about P218 to about M226 (about P223 to about M231 of SEQ ID NO:61) correspond to the highly antigenic regions of the TR14 protein, predicted using the Jameson-Wolf antigenic index (See Figure 11 and Table IV). These highly antigenic fragments correspond to the amino acid residues illustrated in Figure 4A-~~D~~E and in SEQ ID NO:5 (or Figures 10A-H and SEQ ID NO:61, as indicated above). In this context, "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Methods for determining other such antigenic fragments of the TR14 protein are described in detail below.

[0102] The data presented in Figure 3 are also represented in tabular form in Table I. The columns in Table I are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 3 and Table I: "Res": amino acid residue of SEQ ID NO:2 and Figures 1A-~~1C~~D; "Position": position of the corresponding residue within SEQ ID NO:2 and Figures 1A-~~C~~D; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

[0103] The data presented in Figure 9 are also represented in tabular form in Table III. The columns in Table III are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 9 and Table III: "Res": amino acid residue of SEQ ID NO:40 and Figures 7A-~~D~~E; "Position": position of the corresponding residue within SEQ ID NO:40 and Figures 7A-~~D~~E; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

[0108] The above-mentioned preferred regions set out in Figure 3 and in Table I include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figures 1A-D. As set out in Figure 3 and in Table I, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and Hopp-Woods hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions.

[0111] The data presented in Figure 6 are also represented in tabular form in Table II. As above, the columns in Table II are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 6 and Table II: "Res": amino acid residue of SEQ ID NO:5 and Figures 4A-~~D~~E; "Position": position of the corresponding residue within SEQ ID NO:5 and Figures 4A-~~D~~E; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

[0118] The above-mentioned preferred regions set out in Figure 6 and in Table II include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figures 4A-~~D~~E. As set out in Figure 6 and in Table II, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and Hopp-Woods hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions.

[0119] In another aspect, the invention provides an isolated nucleic acid molecule comprising a polynucleotide which hybridizes under stringent hybridization conditions to a portion of the polynucleotide in a TR13 nucleic acid molecule of the invention described above, for instance, the cDNA clone (HWLHM70) contained in ATCC Deposit

No. PTA-349, the nucleic acid sequence disclosed in Figures 1A-~~C~~D or the complementary strand thereof, and fragments thereof (e.g., as described herein).

[0121] In another aspect, the invention provides an isolated nucleic acid molecule comprising a polynucleotide which hybridizes under stringent hybridization conditions to molecule of the invention described above, for instance, the TR13 cDNA clone (HWLHN83) contained in ATCC Deposit No. PTA-507, the nucleic acid sequence disclosed in figures 7A-~~D~~E or the complementary strand thereto, and fragments thereof (e.g., as described herein).

[0126] In another aspect, the invention provides an isolated nucleic acid molecule comprising a polynucleotide which hybridizes under stringent hybridization conditions to a portion of the polynucleotide in a TR14 nucleic acid molecule of the invention described above, for instance, a cDNA clone (HMSHK47) contained in ATCC Deposit No. PTA-348, the nucleic acid sequence disclosed in preferably in Figures 10A-H or, alternatively, in Figures 4A-~~D~~E or the complementary strand thereto, and fragments thereof (e.g., as described herein).

[0130] In further embodiments, nucleic acids of the invention comprise at least 15, at least 30, at least 50, at least 100, or at least 250, at least 500, or at least 1000 contiguous nucleotides of TR13 coding sequence, but consist of less than or equal to 1000 kb, 500 kb, 250 kb, 200 kb, 150 kb, 100 kb, 75 kb, 50 kb, 30 kb, 25 kb, 20 kb, 15 kb, 10 kb, or 5 kb of genomic DNA that flanks the 5' or 3' coding nucleotide set forth in Figures 1A-~~C~~D (SEQ ID NO:1) or in Figures 7A-~~D~~E (SEQ ID NO:39). In further embodiments, nucleic acids of the invention comprise at least 15, at least 30, at least 50, at least 100, or at least 250, at least 500, or at least 1000 contiguous nucleotides of TR13 coding sequence, but do not comprise all or a portion of any TR13 intron. In another embodiment, the nucleic acid comprising TR13 coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the TR13 gene in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[0131] In further, nucleic acids of the invention comprise at least 15, at least 30, at least 50, at least 100, or at least 250, at least 500, or at least 1000 contiguous nucleotides of TR14 coding sequence, but consist of less than or equal to 1000 kb, 500 kb, 250 kb, 200 kb, 150 kb, 100 kb, 75 kb, 50 kb, 30 kb, 25 kb, 20 kb, 15 kb, 10 kb, or 5 kb of genomic

DNA that flanks the 5' or 3' coding nucleotide set forth preferably in Figures 10A-H (SEQ ID NO:60) or, alternatively, in Figures 4A-~~D~~E (SEQ ID NO:4). In further embodiments, nucleic acids of the invention comprise at least 15, at least 30, at least 50, at least 100, or at least 250, at least 500, or at least 1000 contiguous nucleotides of TR14 coding sequence, but do not comprise all or a portion of any TR14 intron. In another embodiment, the nucleic acid comprising TR14 coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the TR14 gene in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[0138] Further embodiments of the invention include isolated nucleic acid molecules comprising or alternatively consisting of, a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98%, or 99% identical to: (a) a nucleotide sequence encoding the polypeptide having the amino acid sequence in SEQ ID NO:2; (b) a nucleotide sequence encoding the polypeptide having the amino acid sequence in SEQ ID NO:2, but lacking the amino terminal methionine (amino acid positions 2 - 750 of SEQ ID NO:2); (c) a nucleotide sequence encoding the polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-349 (HWLHM70); (d) a nucleotide sequence encoding the mature TR13 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-349 (HWLHM70); (e) a nucleotide sequence encoding any combination of one, two, three or all four of the TR13 cysteine rich domains disclosed in Figures 1A-~~C~~D (amino acids 105 to 170, amino acids 251 to 265, amino acids 331 to 410, and/or amino acids 580 to 610 of SEQ ID NO:2); (f) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 105 to about 170 of SEQ ID NO:2; (g) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 251 to about 265 of SEQ ID NO:2; (h) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 331 to about 410 of SEQ ID NO:2; (i) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 580 to about 610 of SEQ ID NO:2; and (j) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i), above. In this

context "about" includes the particularly recited size, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

[0139] Further embodiments of the invention include isolated nucleic acid molecules comprising or alternatively consisting of, a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98%, or 99% identical to: (a) a nucleotide sequence encoding the polypeptide having the amino acid sequence in SEQ ID NO:40; (b) a nucleotide sequence encoding the polypeptide having the amino acid sequence in SEQ ID NO:40, but lacking the amino terminal methionine (amino acid positions 2 - 1001 of SEQ ID NO:40); (c) a nucleotide sequence encoding the polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-507 (HWLHN83); (d) a nucleotide sequence encoding the mature TR13 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-507 (HWLHN83); (e) a nucleotide sequence encoding the TR13 receptor mature extracellular domain (amino acid positions from about 42 to about 906 of SEQ ID NO:40); (f) a nucleotide sequence encoding the TR13 receptor transmembrane domain (amino acid positions from about ~~134~~907 to about ~~150~~931 of SEQ ID NO:40); (g) a nucleotide sequence encoding the TR13 receptor intracellular domain (amino acid positions 932 to about 1001 of SEQ ID NO:40); (h) a nucleotide sequence encoding the TR13 receptor extracellular and intracellular domains with all or a part of the transmembrane domain deleted (amino acid positions from about 42 to about 906 and 932 to about 1001 of SEQ ID NO:40); (i) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 271 to about 421 of SEQ ID NO:40; (j) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 271 to about 286 of SEQ ID NO:40; (k) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 290 to about 300 of SEQ ID NO:40; (l) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 301 to about 320 of SEQ ID NO:40; (m) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 329 to about 361 of SEQ ID NO:40; (n) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 404 to about 421 of SEQ ID NO:40; (o) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 585 to about 595 of

SEQ ID NO:40; (p) a nucleotide sequence encoding any one of the TR13 conserved domains as shown in Figures 7A-~~D~~E; (q) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 661 to about 674 of SEQ ID NO:40; (r) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 710 to about 744 of SEQ ID NO:40; (s) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 980 to about 991 of SEQ ID NO:40; (t) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 45 to about 60 of SEQ ID NO:40; (u) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 121 to about 135 of SEQ ID NO:40; (v) a nucleotide sequence encoding the polypeptide having the amino acid sequence at positions from about 145 to about 160 of SEQ ID NO:40; and (w) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u) or (v) above. In this context "about" includes the particularly recited size, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

[0140] By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a TR13 polypeptide is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five mismatches per each 100 nucleotides of the reference nucleotide sequence encoding the TR13 polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mismatches of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The reference (query) sequence may be the entire TR13 encoding nucleotide sequence shown in Figures 1A-~~C~~D (SEQ ID NO:1) or Figures 7A-~~D~~E (SEQ ID NO:39) or any TR13 polynucleotide fragment (e.g., a polynucleotide encoding the amino acid sequence

of any of the TR13 N- and/or C- terminal deletions described herein), variant, derivative or analog, as described herein.

[0143] By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a TR14 polypeptide is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five mismatches per each 100 nucleotides of the reference nucleotide sequence encoding the TR14 polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mismatches of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The reference (query) sequence may be the entire TR14 encoding nucleotide sequence shown preferably in Figures 10A-H (SEQ ID NO:60) or, alternatively, in Figures 4A-~~D~~E (SEQ ID NO:4) or any TR14 polynucleotide fragment (e.g., a polynucleotide encoding the amino acid sequence of any of the TR14 N- and/or C- terminal deletions described herein), variant, derivative or analog, as described herein.

[0224] Polypeptide fragments of the present invention include polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:2, encoded by the cDNA contained in the clone deposited as ATCC Deposit No. PTA-349, or encoded by a nucleic acid which hybridizes (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone, or shown in Figures 1A-~~C~~D (SEQ ID NO:1) or the complementary strand thereto, or polynucleotide fragments thereof (e.g., as disclosed herein). Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise, or alternatively consist of, from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 351 to 400, 401 to 450, 451 to 500, 501 to 550, 551 to 600,

601 to 650, 651 to 700, and/or 701 to 750 of SEQ ID NO:2. Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[0225] Polypeptide fragments of the present invention include polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:40, encoded by the cDNA contained in the clone deposited as ATCC Deposit No. PTA-507, or encoded by a nucleic acid which hybridizes (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone, or shown in Figures 7A-~~D~~E (SEQ ID NO:40) or the complementary strand thereto or polynucleotide fragments thereof (e.g., as disclosed herein). Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise, or alternatively consist of, from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 351 to 400, 401 to 450, 451 to 500, 501 to 550, 551 to 600, 601 to 650, 651 to 700, 701 to 750, 751 to 800, 801 to 850, 851 to 900, 901 to 950, and/or 951 to 1001 of SEQ ID NO:2. Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1001 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[0228] In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively consist of, one or more domains of the TR13 polypeptide disclosed in Figures 1A-~~C~~D. Preferred polypeptide fragments of the present invention include a member selected from the group: (a) a polypeptide comprising or alternatively, consisting of, any combination of one, two, three, or all four of the TR13 cysteine rich domains disclosed in Figures 1A-~~C~~D (predicted to constitute amino acid residues from

about 105 to about 170, about 251 to about 265, about 331 to about 410, and about 580 to about 610 of SEQ ID NO:2); (b) a polypeptide comprising, or alternatively, consisting of, one, two, three, four or more, epitope bearing portions of the TR13 receptor protein disclosed in Figures 1A-~~C~~D (for example, those epitope bearing portions predicted to constitute amino acid residues from about 1 to about 170, or about 210 to about 318, or about 343 to about 480, or about 548 to about 592, or about 632 to about 742 of SEQ ID NO:2); (c) any combination of polypeptides (a)-(c). Polynucleotides encoding these polypeptides are also encompassed by the invention. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[0229] In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively consist of, one or more domains of the TR13 polypeptide disclosed in Figure 7A-~~D~~E. Preferred polypeptide fragments of the present invention include a member selected from the group: (a) a polypeptide comprising, or alternatively consisting of, amino acids 1 to about 41 of SEQ ID NO:40; (b) a polypeptide comprising, or alternatively consisting of, amino acids 42 to about 906 of SEQ ID NO:40; (c) a polypeptide comprising, or alternatively consisting of, amino acids 907 to about 931 of SEQ ID NO:40; (d) a polypeptide comprising, or alternatively consisting of, amino acids 932 to about 1001 of SEQ ID NO:40; (e) a polypeptide comprising or alternatively, consisting of, any combination of one, two, three, four or more of the TR13 cysteine rich domains disclosed in Figures 7A-~~D~~E (predicted to constitute amino acid residues from about 271 to about 421, 271 to about 286, about 290 to about 300, about 301 to about 320, about 329 to about 361, about 404 to about 421, about 585 to about 595 of SEQ ID NO:40); (f) a polypeptide comprising, or alternatively, consisting of, one, two, three, four or more, epitope bearing portions of the TR13 receptor protein disclosed in Figures 7A-~~D~~E (for example, these epitope bearing portions predicted to constitute amino acid residues from about 1 to about 262, or about 264 to about 423, or about 437 to about 789, or about 791 to about 1001, of SEQ ID NO:40); and (g) any combination of polypeptides (a)-(f). In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0230] As discussed above, it is believed that the extracellular cysteine rich motifs of TR13 are important for interactions between TR13 and its ligands. Accordingly, in preferred embodiments, polypeptide fragments of the invention comprise, or alternatively consist of amino acid residues from about 105 to about 170, about 251 to about 265, about 331 to about 410 and/or about 580 to about 610 of the amino acid sequence disclosed in Figures 1A-~~C~~D (SEQ ID NO:2). In a specific embodiment the polypeptides of the invention comprise, or alternatively consist of any combination of one, two, three or all four extracellular cysteine rich motifs disclosed in Figures 1A-~~C~~D. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0231] As discussed above, it is believed that the extracellular cysteine rich motifs of TR13 are important for interactions between TR13 and its ligands. Accordingly, in preferred embodiments, polypeptide fragments of the invention comprise, or alternatively consist of amino acid residues from about 271 to about 421, or 271 to about 286, or about 290 to about 300, or about 301 to about 320, or about 329 to about 361, or about 404 to about 421, or about 585 to about 595 of the amino acid sequence disclosed in Figures 7A-~~D~~E (SEQ ID NO:40). In a specific embodiment the polypeptides of the invention comprise, or alternatively consist of any combination of one, two, three, four or more of the extracellular cysteine rich motifs disclosed in Figures 7A-~~D~~E. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0232] Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of TR13 (SEQ ID NO:2 or SEQ ID NO:40). Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program)

of complete (i.e., full-length) TR13 (SEQ ID NO:2 or SEQ ID NO:40). Certain preferred regions are those set out in Figure 3 (Table I) and Figure 9 (Table III) and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in Figures 1A-~~C~~D (SEQ ID NO:2) or Figures 7A-~~D~~E (SEQ ID NO:40), respectively. Such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle predicted hydrophilic and Hopp-Woods predicted hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0234] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the TR13 amino acid sequence shown in Figures 1A-~~C~~D, up to the aspartic acid residue at position number 745 and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-750 of Figures 1A-~~C~~D, where n^1 is an integer from 2 to 745 corresponding to the position of the amino acid residue in Figures 1A-~~C~~D (which is identical to the sequence shown as SEQ ID NO:2). In a specific embodiment, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-750 of Figures 1A-~~C~~D, where n^1 is an integer from 2 to 610 corresponding to the position of the amino acid residue in Figures 1A-~~C~~D. Polynucleotides encoding these polypeptides are also encompassed.

[0235] In one embodiment, N-terminal deletions of the TR13 polypeptides of the invention can be described by the general formula n^2-750, where n^2 is a number from 2 to 745, corresponding to the position of amino acid identified in Figures 1A-~~C~~D (SEQ ID NO:2). N-terminal deletions of the TR13 polypeptide of the invention shown as SEQ ID NO:2 include polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: D-2 to R-750; Q-3 to R-750; S-4 to R-750; T-5 to R-750; Q-6 to R-750; A-7 to R-750; C-8 to R-750; A-9 to R-750; G-10 to R-750; E-11 to R-750; K-12 to R-750; H-13 to R-750; C-14 to R-750; H-15 to R-750; N-16 to R-750; R-17 to R-750; G-18 to R-750; G-19 to R-750; L-20 to R-750; H-21 to R-750; F-22 to R-750; R-23 to R-

750; M-24 to R-750; L-25 to R-750; P-26 to R-750; L-27 to R-750; Q-28 to R-750; T-29 to R-750; W-30 to R-750; H-31 to R-750; V-32 to R-750; C-33 to R-750; R-34 to R-750; Q-35 to R-750; A-36 to R-750; G-37 to R-750; L-38 to R-750; L-39 to R-750; F-40 to R-750; L-41 to R-750; Q-42 to R-750; T-43 to R-750; L-44 to R-750; P-45 to R-750; S-46 to R-750; N-47 to R-750; S-48 to R-750; Y-49 to R-750; S-50 to R-750; N-51 to R-750; K-52 to R-750; G-53 to R-750; E-54 to R-750; T-55 to R-750; S-56 to R-750; C-57 to R-750; H-58 to R-750; Q-59 to R-750; C-60 to R-750; D-61 to R-750; P-62 to R-750; D-63 to R-750; K-64 to R-750; Y-65 to R-750; S-66 to R-750; E-67 to R-750; K-68 to R-750; G-69 to R-750; S-70 to R-750; S-71 to R-750; S-72 to R-750; C-73 to R-750; N-74 to R-750; V-75 to R-750; R-76 to R-750; P-77 to R-750; A-78 to R-750; C-79 to R-750; T-80 to R-750; D-81 to R-750; K-82 to R-750; D-83 to R-750; Y-84 to R-750; F-85 to R-750; Y-86 to R-750; T-87 to R-750; H-88 to R-750; T-89 to R-750; A-90 to R-750; C-91 to R-750; D-92 to R-750; A-93 to R-750; N-94 to R-750; G-95 to R-750; E-96 to R-750; T-97 to R-750; Q-98 to R-750; L-99 to R-750; M-100 to R-750; Y-101 to R-750; K-102 to R-750; W-103 to R-750; A-104 to R-750; K-105 to R-750; P-106 to R-750; K-107 to R-750; I-108 to R-750; C-109 to R-750; S-110 to R-750; E-111 to R-750; D-112 to R-750; L-113 to R-750; E-114 to R-750; G-115 to R-750; A-116 to R-750; V-117 to R-750; K-118 to R-750; L-119 to R-750; P-120 to R-750; A-121 to R-750; S-122 to R-750; G-123 to R-750; V-124 to R-750; K-125 to R-750; T-126 to R-750; H-127 to R-750; C-128 to R-750; P-129 to R-750; P-130 to R-750; C-131 to R-750; N-132 to R-750; P-133 to R-750; G-134 to R-750; F-135 to R-750; F-136 to R-750; K-137 to R-750; T-138 to R-750; N-139 to R-750; N-140 to R-750; S-141 to R-750; T-142 to R-750; C-143 to R-750; Q-144 to R-750; P-145 to R-750; C-146 to R-750; P-147 to R-750; Y-148 to R-750; G-149 to R-750; S-150 to R-750; Y-151 to R-750; S-152 to R-750; N-153 to R-750; G-154 to R-750; S-155 to R-750; D-156 to R-750; C-157 to R-750; T-158 to R-750; R-159 to R-750; C-160 to R-750; P-161 to R-750; A-162 to R-750; G-163 to R-750; T-164 to R-750; E-165 to R-750; P-166 to R-750; A-167 to R-750; V-168 to R-750; G-169 to R-750; F-170 to R-750; E-171 to R-750; Y-172 to R-750; K-173 to R-750; W-174 to R-750; W-175 to R-750; N-176 to R-750; T-177 to R-750; L-178 to R-750; P-179 to R-750; T-180 to R-750; N-181 to R-750; M-182 to R-750; E-183 to R-750; T-184 to R-750; T-185 to R-750; V-186 to R-750; L-187 to R-750; S-188 to R-750; G-189 to R-750; I-190 to R-750; N-191 to R-750; F-192 to R-750; E-193 to R-750; Y-194 to R-750; K-195 to R-750; G-196 to R-750; M-197 to R-

750; T-198 to R-750; G-199 to R-750; W-200 to R-750; E-201 to R-750; V-202 to R-750; A-203 to R-750; G-204 to R-750; D-205 to R-750; H-206 to R-750; I-207 to R-750; Y-208 to R-750; T-209 to R-750; A-210 to R-750; A-211 to R-750; G-212 to R-750; A-213 to R-750; S-214 to R-750; D-215 to R-750; N-216 to R-750; D-217 to R-750; F-218 to R-750; M-219 to R-750; I-220 to R-750; L-221 to R-750; T-222 to R-750; L-223 to R-750; V-224 to R-750; V-225 to R-750; P-226 to R-750; G-227 to R-750; F-228 to R-750; R-229 to R-750; P-230 to R-750; P-231 to R-750; Q-232 to R-750; S-233 to R-750; V-234 to R-750; M-235 to R-750; A-236 to R-750; D-237 to R-750; T-238 to R-750; E-239 to R-750; N-240 to R-750; K-241 to R-750; E-242 to R-750; V-243 to R-750; A-244 to R-750; R-245 to R-750; I-246 to R-750; T-247 to R-750; F-248 to R-750; V-249 to R-750; F-250 to R-750; E-251 to R-750; T-252 to R-750; L-253 to R-750; C-254 to R-750; S-255 to R-750; V-256 to R-750; N-257 to R-750; C-258 to R-750; E-259 to R-750; L-260 to R-750; Y-261 to R-750; F-262 to R-750; M-263 to R-750; V-264 to R-750; G-265 to R-750; V-266 to R-750; N-267 to R-750; S-268 to R-750; R-269 to R-750; T-270 to R-750; N-271 to R-750; T-272 to R-750; P-273 to R-750; V-274 to R-750; E-275 to R-750; T-276 to R-750; W-277 to R-750; K-278 to R-750; G-279 to R-750; S-280 to R-750; K-281 to R-750; G-282 to R-750; K-283 to R-750; Q-284 to R-750; S-285 to R-750; Y-286 to R-750; T-287 to R-750; Y-288 to R-750; I-289 to R-750; I-290 to R-750; E-291 to R-750; E-292 to R-750; N-293 to R-750; T-294 to R-750; T-295 to R-750; T-296 to R-750; S-297 to R-750; F-298 to R-750; T-299 to R-750; W-300 to R-750; A-301 to R-750; F-302 to R-750; Q-303 to R-750; R-304 to R-750; T-305 to R-750; T-306 to R-750; F-307 to R-750; H-308 to R-750; E-309 to R-750; A-310 to R-750; S-311 to R-750; R-312 to R-750; K-313 to R-750; Y-314 to R-750; T-315 to R-750; N-316 to R-750; D-317 to R-750; V-318 to R-750; A-319 to R-750; K-320 to R-750; I-321 to R-750; Y-322 to R-750; S-323 to R-750; I-324 to R-750; N-325 to R-750; V-326 to R-750; T-327 to R-750; N-328 to R-750; V-329 to R-750; M-330 to R-750; N-331 to R-750; G-332 to R-750; V-333 to R-750; A-334 to R-750; S-335 to R-750; Y-336 to R-750; C-337 to R-750; R-338 to R-750; P-339 to R-750; C-340 to R-750; A-341 to R-750; L-342 to R-750; E-343 to R-750; A-344 to R-750; S-345 to R-750; D-346 to R-750; V-347 to R-750; G-348 to R-750; S-349 to R-750; S-350 to R-750; C-351 to R-750; T-352 to R-750; S-353 to R-750; C-354 to R-750; P-355 to R-750; A-356 to R-750; G-357 to R-750; Y-358 to R-750; Y-359 to R-750; I-360 to R-750; D-361 to R-750; R-362 to R-750; D-363 to R-750; S-364 to R-750; G-365 to R-750; T-366 to R-750;

C-367 to R-750; H-368 to R-750; S-369 to R-750; C-370 to R-750; P-371 to R-750; P-372 to R-750; N-373 to R-750; T-374 to R-750; I-375 to R-750; L-376 to R-750; K-377 to R-750; A-378 to R-750; H-379 to R-750; Q-380 to R-750; P-381 to R-750; Y-382 to R-750; G-383 to R-750; V-384 to R-750; Q-385 to R-750; A-386 to R-750; C-387 to R-750; V-388 to R-750; P-389 to R-750; C-390 to R-750; G-391 to R-750; P-392 to R-750; G-393 to R-750; T-394 to R-750; K-395 to R-750; N-396 to R-750; N-397 to R-750; K-398 to R-750; I-399 to R-750; H-400 to R-750; S-401 to R-750; L-402 to R-750; C-403 to R-750; Y-404 to R-750; N-405 to R-750; D-406 to R-750; C-407 to R-750; T-408 to R-750; F-409 to R-750; S-410 to R-750; R-411 to R-750; N-412 to R-750; T-413 to R-750; P-414 to R-750; T-415 to R-750; R-416 to R-750; T-417 to R-750; F-418 to R-750; N-419 to R-750; Y-420 to R-750; N-421 to R-750; F-422 to R-750; S-423 to R-750; A-424 to R-750; L-425 to R-750; A-426 to R-750; N-427 to R-750; T-428 to R-750; V-429 to R-750; T-430 to R-750; L-431 to R-750; A-432 to R-750; G-433 to R-750; G-434 to R-750; P-435 to R-750; S-436 to R-750; F-437 to R-750; T-438 to R-750; S-439 to R-750; K-440 to R-750; G-441 to R-750; L-442 to R-750; K-443 to R-750; Y-444 to R-750; F-445 to R-750; H-446 to R-750; H-447 to R-750; F-448 to R-750; T-449 to R-750; L-450 to R-750; S-451 to R-750; L-452 to R-750; C-453 to R-750; G-454 to R-750; N-455 to R-750; Q-456 to R-750; G-457 to R-750; R-458 to R-750; K-459 to R-750; M-460 to R-750; S-461 to R-750; V-462 to R-750; C-463 to R-750; T-464 to R-750; D-465 to R-750; N-466 to R-750; V-467 to R-750; T-468 to R-750; D-469 to R-750; L-470 to R-750; R-471 to R-750; I-472 to R-750; P-473 to R-750; E-474 to R-750; G-475 to R-750; E-476 to R-750; S-477 to R-750; G-478 to R-750; F-479 to R-750; S-480 to R-750; K-481 to R-750; S-482 to R-750; I-483 to R-750; T-484 to R-750; A-485 to R-750; Y-486 to R-750; V-487 to R-750; C-488 to R-750; Q-489 to R-750; A-490 to R-750; V-491 to R-750; I-492 to R-750; I-493 to R-750; P-494 to R-750; P-495 to R-750; E-496 to R-750; V-497 to R-750; T-498 to R-750; G-499 to R-750; Y-500 to R-750; K-501 to R-750; A-502 to R-750; G-503 to R-750; V-504 to R-750; S-505 to R-750; S-506 to R-750; Q-507 to R-750; P-508 to R-750; V-509 to R-750; S-510 to R-750; L-511 to R-750; A-512 to R-750; D-513 to R-750; R-514 to R-750; L-515 to R-750; I-516 to R-750; G-517 to R-750; V-518 to R-750; T-519 to R-750; T-520 to R-750; D-521 to R-750; M-522 to R-750; T-523 to R-750; L-524 to R-750; D-525 to R-750; G-526 to R-750; I-527 to R-750; T-528 to R-750; S-529 to R-750; P-530 to R-750; A-531 to R-750; E-532 to R-750; L-533 to R-750; F-534 to R-750; H-535 to R-

750; L-536 to R-750; E-537 to R-750; S-538 to R-750; L-539 to R-750; G-540 to R-750; I-541 to R-750; P-542 to R-750; D-543 to R-750; V-544 to R-750; I-545 to R-750; F-546 to R-750; F-547 to R-750; Y-548 to R-750; R-549 to R-750; S-550 to R-750; N-551 to R-750; D-552 to R-750; V-553 to R-750; T-554 to R-750; Q-555 to R-750; S-556 to R-750; C-557 to R-750; S-558 to R-750; S-559 to R-750; G-560 to R-750; R-561 to R-750; S-562 to R-750; T-563 to R-750; T-564 to R-750; I-565 to R-750; R-566 to R-750; V-567 to R-750; R-568 to R-750; C-569 to R-750; S-570 to R-750; P-571 to R-750; Q-572 to R-750; K-573 to R-750; T-574 to R-750; V-575 to R-750; P-576 to R-750; G-577 to R-750; S-578 to R-750; L-579 to R-750; L-580 to R-750; L-581 to R-750; P-582 to R-750; G-583 to R-750; T-584 to R-750; C-585 to R-750; S-586 to R-750; D-587 to R-750; G-588 to R-750; T-589 to R-750; C-590 to R-750; D-591 to R-750; G-592 to R-750; C-593 to R-750; N-594 to R-750; F-595 to R-750; H-596 to R-750; F-597 to R-750; L-598 to R-750; W-599 to R-750; E-600 to R-750; S-601 to R-750; A-602 to R-750; A-603 to R-750; A-604 to R-750; C-605 to R-750; P-606 to R-750; L-607 to R-750; C-608 to R-750; S-609 to R-750; V-610 to R-750; A-611 to R-750; D-612 to R-750; Y-613 to R-750; H-614 to R-750; A-615 to R-750; I-616 to R-750; V-617 to R-750; S-618 to R-750; S-619 to R-750; C-620 to R-750; V-621 to R-750; A-622 to R-750; G-623 to R-750; I-624 to R-750; Q-625 to R-750; K-626 to R-750; T-627 to R-750; T-628 to R-750; Y-629 to R-750; V-630 to R-750; W-631 to R-750; R-632 to R-750; E-633 to R-750; P-634 to R-750; K-635 to R-750; L-636 to R-750; C-637 to R-750; S-638 to R-750; G-639 to R-750; G-640 to R-750; I-641 to R-750; S-642 to R-750; L-643 to R-750; P-644 to R-750; E-645 to R-750; Q-646 to R-750; R-647 to R-750; V-648 to R-750; T-649 to R-750; I-650 to R-750; C-651 to R-750; K-652 to R-750; T-653 to R-750; I-654 to R-750; D-655 to R-750; F-656 to R-750; W-657 to R-750; L-658 to R-750; K-659 to R-750; V-660 to R-750; G-661 to R-750; I-662 to R-750; S-663 to R-750; A-664 to R-750; G-665 to R-750; T-666 to R-750; C-667 to R-750; T-668 to R-750; A-669 to R-750; I-670 to R-750; L-671 to R-750; L-672 to R-750; T-673 to R-750; V-674 to R-750; L-675 to R-750; T-676 to R-750; C-677 to R-750; Y-678 to R-750; F-679 to R-750; W-680 to R-750; K-681 to R-750; K-682 to R-750; N-683 to R-750; Q-684 to R-750; K-685 to R-750; L-686 to R-750; E-687 to R-750; Y-688 to R-750; K-689 to R-750; Y-690 to R-750; S-691 to R-750; K-692 to R-750; L-693 to R-750; V-694 to R-750; M-695 to R-750; N-696 to R-750; A-697 to R-750; T-698 to R-750; L-699 to R-750; K-700 to R-750; D-701 to R-750; C-702 to R-750; D-703 to R-750; L-704 to R-750;

P-705 to R-750; A-706 to R-750; A-707 to R-750; D-708 to R-750; S-709 to R-750; C-710 to R-750; A-711 to R-750; I-712 to R-750; M-713 to R-750; E-714 to R-750; G-715 to R-750; E-716 to R-750; D-717 to R-750; V-718 to R-750; E-719 to R-750; D-720 to R-750; D-721 to R-750; L-722 to R-750; I-723 to R-750; F-724 to R-750; T-725 to R-750; S-726 to R-750; K-727 to R-750; N-728 to R-750; H-729 to R-750; S-730 to R-750; L-731 to R-750; G-732 to R-750; R-733 to R-750; S-734 to R-750; N-735 to R-750; H-736 to R-750; L-737 to R-750; P-738 to R-750; P-739 to R-750; R-740 to R-750; G-741 to R-750; L-742 to R-750; L-743 to R-750; M-744 to R-750; D-745 to R-750; of SEQ ID NO:2. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0236] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the TR13 amino acid sequence shown in Figures 7A-~~D~~E, up to the aspartic acid residue at position number 996 and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-1001 of Figures 7A-~~D~~E, where n^1 is an integer from 2 to 996 corresponding to the position of the amino acid residue in Figures 7A-~~C~~E (which is identical to the sequence shown as SEQ ID NO:40). In a specific embodiment, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-906 of Figures 7A-~~D~~E where n^1 is an integer from 42 to 595 corresponding to the position of the amino acid residue in Figures 7A-~~D~~E. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0237] In another embodiment, N-terminal deletions of the TR13 polypeptide can be described by the general formula n^2-1001, where n^2 is a number from 2 to 996, corresponding to the position of amino acid identified in Figures 7A-~~D~~E (SEQ ID NO:40). N-terminal deletions of the TR13 polypeptide of the invention shown as SEQ ID NO:40 include polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: A-2 to R-1001; E-3 to R-1001; P-4 to R-1001; G-5 to R-1001; H-6 toR-1001; S-7 to R-1001; H-8 to R-1001; H-9 to R-1001; L-10 to R-1001; S-11 to R-1001; A-12 to R-1001; R-13 to R-1001;V-14 to R-1001; R-15 to R-1001; G-16 to R-1001; R-17 to R-1001; T-18 to R-1001; E-19 to R-1001; R-20 to R-1001;R-21 to R-1001; I-22 to R-1001; P-23 to R-1001; R-24 to R-1001; L-25 to R-1001; W-26 to R-1001; R-27 to R-1001; L-28to R-1001; L-29 to R-1001; L-30 to R-1001; W-31 to R-1001; A-32 to R-1001; G-33 to R-

1001; T-34 to R-1001; A-35 toR-1001; F-36 to R-1001; Q-37 to R-1001; V-38 to R-1001; T-39 to R-1001; Q-40 to R-1001; G-41 to R-1001; T-42 toR-1001; G-43 to R-1001; P-44 to R-1001; E-45 to R-1001; L-46 to R-1001; H-47 to R-1001; A-48 to R-1001; C-49 toR-1001; K-50 to R-1001; E-51 to R-1001; S-52 to R-1001; E-53 to R-1001; Y-54 to R-1001; H-55 to R-1001; Y-56 toR-1001; E-57 to R-1001; Y-58 to R-1001; T-59 to R-1001; A-60 to R-1001; C-61 to R-1001; D-62 to R-1001; S-63 toR-1001; T-64 to R-1001; G-65 to R-1001; S-66 to R-1001; R-67 to R-1001; W-68 to R-1001; R-69 to R-1001; V-70 toR-1001; A-71 to R-1001; V-72 to R-1001; P-73 to R-1001; H-74 to R-1001; T-75 to R-1001; P-76 to R-1001; G-77 toR-1001; L-78 to R-1001; C-79 to R-1001; T-80 to R-1001; S-81 to R-1001; L-82 to R-1001; P-83 to R-1001; D-84 toR-1001; P-85 to R-1001; V-86 to R-1001; K-87 to R-1001; G-88 to R-1001; T-89 to R-1001; E-90 to R-1001; C-91 toR-1001; S-92 to R-1001; F-93 to R-1001; S-94 to R-1001; C-95 to R-1001; N-96 to R-1001; A-97 to R-1001; G-98 toR-1001; E-99 to R-1001; F-100 to R-1001; L-101 to R-1001; D-102 to R-1001; M-103 to R-1001; K-104 to R-1001; D-105to R-1001; Q-106 to R-1001; S-107 to R-1001; C-108 to R-1001; K-109 to R-1001; P-110 to R-1001; C-111 to R-1001;A-112 to R-1001; E-113 to R-1001; G-114 to R-1001; R-115 to R-1001; Y-116 to R-1001; S-117 to R-1001; L-118 toR-1001; G-119 to R-1001; T-120 to R-1001; G-121 to R-1001; I-122 to R-1001; R-123 to R-1001; F-124 to R-1001;D-125 to R-1001; E-126 to R-1001; W-127 to R-1001; D-128 to R-1001; E-129 to R-1001; L-130 to R-1001; P-131 toR-1001; H-132 to R-1001; G-133 to R-1001; F-134 to R-1001; A-135 to R-1001; S-136 to R-1001; L-137 to R-1001;S-138 to R-1001; A-139 to R-1001; N-140 to R-1001; M-141 to R-1001; E-142 to R-1001; L-143 to R-1001; D-144 toR-1001; D-145 to R-1001; S-146 to R-1001; A-147 to R-1001; A-148 to R-1001; E-149 to R-1001; S-150 to R-1001;T-151 to R-1001; G-152 to R-1001; N-153 to R-1001; C-154 to R-1001; T-155 to R-1001; S-156 to R-1001; S-157 toR-1001; K-158 to R-1001; W-159 to R-1001; V-160 to R-1001; P-161 to R-1001; R-162 to R-1001; G-163 to R-1001;D-164 to R-1001; Y-165 to R-1001; I-166 to R-1001; A-167 to R-1001; F-168 to R-1001; N-169 to R-1001; T-170 toR-1001; D-171 to R-1001; E-172 to R-1001; C-173 to R-1001; T-174 to R-1001; A-175 to R-1001; T-176 to R-1001;L-177 to R-1001; M-178 to R-1001; Y-179 to R-1001; A-180 to R-1001; V-181 to R-1001; N-182 to R-1001; L-183 toR-1001; K-184 to R-1001; Q-185 to R-1001; S-186 to R-1001; G-187 to R-1001; T-188 to R-1001; V-189 to R-1001;N-190 to R-1001; F-191 to R-1001; E-192 to R-1001; Y-193 to R-1001; Y-194 to R-1001; Y-195 to R-1001; P-196 toR-1001; D-

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to R-1001; L-993 to R-1001;L-994 to R-1001; M-995 to R-1001; D-996 to R-1001; of SEQ ID NO:40. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0239] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the TR13 polypeptide shown in Figures 1A-~~C~~D (SEQ ID NO:2), up to the glutamine residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m^1 of Figures 1A-~~C~~D, where m^1 is an integer from 6 to 749 corresponding to the position of the amino acid residue in Figures 1A-~~C~~D.

[0241] The present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the TR13 polypeptide shown in Figures 7A-~~D~~E (SEQ ID NO:40), up to the histidine residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m^1 of Figures 7A-~~D~~E, where m^1 is an integer from 6 to 1001 corresponding to the position of the amino acid residue in Figures 7A-~~D~~E.

[0243] In another embodiment, N-terminal deletions of the predicted extracellular domain of the predicted mature TR13 protein, with the amino acid sequence shown in Figures 7A-~~D~~E, can be described by the general formula n^2-906, where n^2 is a number from 2 to 900, corresponding to the position of amino acid identified in Figures 7A-~~D~~E (SEQ ID NO:40). N-terminal deletions of the TR13 polypeptide of the invention shown as SEQ ID NO:40 include polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: T-42 to D-906; G-43 to D-906; P-44 to D-906; E-45 to D-906; L-46 to D-906; H-47 to D-906; A-48 to D-906; C-49 to D-906; K-50 to D-906; E-51 to D-906; S-52 to D-906; E-53 to D-906; Y-54 to D-906; H-55 to D-906; Y-56 toD-906; E-57 to D-906; Y-58 to D-906; T-59 to D-906; A-60 to D-906; C-61 to D-906; D-62 to D-906; S-63 toD-906; T-64 to D-906; G-65 to D-906; S-66 to D-906; R-67 to D-906; W-68 to D-906; R-69 to D-906; V-70 toD-906; A-71 to D-906; V-72 to D-906; P-73 to D-906; H-74 to D-906; T-75 to D-906; P-76 to D-906; G-77 toD-906; L-78 to D-906; C-79 to D-906; T-80 to D-906; S-81 to D-906; L-82 to D-906; P-83 to D-906; D-84 to D-906; P-85 to D-906; V-86 to D-906; K-87 to D-906; G-88 to D-906; T-89 to D-906; E-90 to D-906; C-91

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[0244] The present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the predicted extracellular domain of the predicted mature TR13 protein, with the amino acid sequence shown in Figures 7A-~~D~~E (SEQ ID NO:40), up to the alanine residue at position number 48, and polynucleotides

encoding such polypeptides. In particular, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 42-m^1 of Figures 7A-~~D~~E, where m^1 is an integer from 48 to 906 corresponding to the position of the amino acid residue in Figures 7A-~~D~~E.

[0246] The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues n^1- m^1 and/or n^2- m^1 of Figures 1A-~~C~~D (i.e., SEQ ID NO:2), where n^1, n^2, and m^1 are integers as described above. Thus, any of the above listed N- or C-terminal deletions can be combined to produce an N- and C-terminal deleted TR13 polypeptide.

[0247] The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues n^1- m^1 and/or n^2- m^1 of Figures 7A-~~D~~E (SEQ ID NO:40), where n^1, n^2, and m^1 are integers as described above. Thus, any of the above listed N- or C-terminal deletions can be combined to produce an N- and C-terminal deleted TR13 polypeptide.

[0253] In specific embodiments, the number of substitutions, additions or deletions in the amino acid sequence of Figures 1A-~~C~~D or Figures 7A-~~D~~E and/or any of the polypeptide fragments described herein (e.g., one or more of the cysteine rich domains, the mature extracellular domain, etc.) is 75, 70, 60, 50, 40, 35, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 30-20, 20-15, 20-10, 15-10, 10-1, 5-10, 1-5, 1-3 or 1-2.

[0258] The polypeptides of the present invention include a polypeptide comprising, or alternatively, consisting of the polypeptide encoded by the cDNA deposited as ATCC Deposit No. PTA-349, including the leader; a polypeptide comprising, or alternatively, consisting of the mature polypeptide encoded by the deposited cDNA minus the leader (i.e., the mature protein); a polypeptide comprising, or alternatively, consisting of amino acids from about 1 to about 750 of SEQ ID NO:2; a polypeptide comprising, or alternatively, consisting of amino acids from about 2 to about 750 of SEQ ID NO:2; a polypeptide comprising, or alternatively, consisting of amino acids from about 1 to about 331 in SEQ ID NO:2; a polypeptide comprising, or alternatively, consisting of any one or more of the four cysteine rich domains disclosed in Figures 1A-~~C~~D (predicted to constitute amino acids from about 105 to about 170, 251 to about 265, about 331 to about 410, and about 580 to about 610 of SEQ ID NO:2); as well as polypeptides which are at least 80% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%,

97%, 98%, or 99% identical to the polypeptides described above (e.g., the polypeptide encoded by the deposited cDNA clone, the polypeptide of Figures 1A-~~C~~D (SEQ ID NO:2) and polypeptide fragments thereof such as disclosed herein), and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2,or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0259] The polypeptides of the present invention include a polypeptide comprising, or alternatively, consisting of the polypeptide encoded by the cDNA deposited as ATCC Deposit No. PTA-507, including the leader; a polypeptide comprising, or alternatively, consisting of the mature polypeptide encoded by the deposited cDNA minus the leader (i.e., the mature protein); a polypeptide comprising, or alternatively, consisting of amino acids from about 1 to about 1001 of SEQ ID NO:40; a polypeptide comprising, or alternatively, consisting of amino acids from about 2 to about 1001 of SEQ ID NO:40; a polypeptide comprising, or alternatively, consisting of amino acids from about 1 to about 906 in SEQ ID NO:40; a polypeptide comprising, or alternatively, consisting of amino acids from about 42 to about 1001 in SEQ ID NO:40; a polypeptide comprising, or alternatively, consisting of amino acids from about 42 to about 906 in SEQ ID NO:40; a polypeptide comprising, or alternatively, consisting of amino acids from about 907 to about 931 in SEQ ID NO:40; a polypeptide comprising, or alternatively, consisting of amino acids from about 932 to about 1001 in SEQ ID NO:40; a polypeptide comprising, or alternatively, consisting of any of the seven cysteine rich domains disclosed in Figures 7A-~~D~~E (predicted to constitute amino acids from about 271 to about 421, 271 to about 286, about 290 to about 300, about 301 to about 320, about 329 to about 361, about 404 to about 421, and about 585 to about 595 of SEQ ID NO:40); as well as polypeptides which are at least 80% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98%, or 99% identical to the polypeptides described above (e.g., the polypeptide encoded by the deposited cDNA clone, the polypeptide of Figures 7A-~~D~~E (SEQ ID NO:40) and polypeptide fragments thereof, such as those disclosed herein), and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2,or 1) amino acids, at either extreme

or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0263] The present application is also directed to proteins comprising, or alternatively consisting of, a polypeptide sequence at least 90%, 95%, 96%, 97%, 98% or 99% identical to the TR13 polypeptide sequence set forth as n^1-m^1, and/or n^2- m^1 for polypeptide sequence shown in Figure 1A-~~C~~D or Figure 7A-~~D~~E herein. In preferred embodiments, the application is directed to proteins comprising, or alternatively consisting of, a polypeptide sequence at least 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific TR13 N- and C-terminal deletions recited herein. Additional preferred embodiments are directed to fusion proteins comprising these polypeptide sequences. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0267] Non-limiting examples of predicted antigenic polypeptides that can be used to generate TR13 receptor-specific antibodies include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about 1 to about 170 in Figures 1A-~~C~~D (corresponding to about amino acid 1 to about 170 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 210 to about 318 in Figures 1A-~~C~~D (corresponding to about amino acid 210 to about 318 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 343 to about 480 in Figures 1A-~~C~~D (corresponding to about amino acid 343 to about 480 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 548 to about 592 in Figures 1A-~~C~~D (corresponding to about amino acid 548 to about 592 in SEQ ID NO:2); and a polypeptide comprising amino acid residues from about 632 to about 742 in Figures 1A-~~C~~D (corresponding to about amino acid 632 to about 742 in SEQ ID NO:2). As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the TR13 receptor protein. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0268] Additional non-limiting examples of predicted antigenic polypeptides that can be used to generate TR13 receptor-specific antibodies include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about ~~about~~ M1 to

about A9, about K12 to about L20, about N47 to about T55, about H58 to about S66, about D63 to about S71, about P77 to about F85, about A90 to about Q98, about F136 to about Q144, about S152 to about C160, about R159 to about A167, about A211 to about M219, about M235 to about V243, about V266 to about V274, about W277 to about S285, about I290 to about F298, about A310 to about V318, about E343 to about C351, about I360 to about H368, about G391 to about I399, about F409 to about T417, about S436 to about Y444, about C453 to about S461, about I472 to about S480, about Y548 to about S556, about C557 to about I565, about V567 to about V575, about T584 to about G592, about R632 to about G640, about W680 to about Y688, about Q684 to about K692, about T698 to about A706, about S726 to about S734, and about S734 to about L742 of SEQ ID NO:2 (Figures 1A-~~C~~D) correspond to the highly antigenic regions of the TR13 protein, predicted using the Jameson-Wolf antigenic index (See Figure 3 and Table I). These highly antigenic fragments correspond to the amino acid residues illustrated in Figure 1A-~~C~~D and in SEQ ID NO:2. As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the TR13 receptor protein. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0269] Non-limiting examples of predicted antigenic polypeptides that can be used to generate TR13-specific antibodies include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about 1 to about 262 in Figures 7A-~~D~~E (corresponding to about amino acid 1 to about 262 in SEQ ID NO:40); a polypeptide comprising amino acid residues from about 264 to about 423 in Figures 7A-~~D~~E (corresponding to about amino acid 264 to about 423 in SEQ ID NO:40); a polypeptide comprising amino acid residues from about 437 to about 789 in Figures 7A-~~D~~E (corresponding to about amino acid 437 to about 789 in SEQ ID NO:40); and a polypeptide comprising amino acid residues from about 791 to about 1001 in Figures 7A-~~D~~E (corresponding to about amino acid 791 to about 1001 in SEQ ID NO:40). As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the TR13 receptor protein. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at

either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0270] Additional non-limiting examples of predicted antigenic polypeptides that can be used to generate TR13 receptor-specific antibodies include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about ~~about~~ M1 to about H9, about V14 to about I22, about H47 to about H55, about C61 to about R69, about L82 to about E90, about D102 to about P110, about K109 to about S117, about F124 to about H132, about M141 to about E149, about S146 to about C154, about S157 to about W165, about F168 to about T176, about N182 to about N190, about Q207 to about A215, about P213 to about M221, about M221 to about E229, about V233 to about V241, about T253 to about V261, about T282 to about S290, about N298 to about T306, about C308 to about Y316, about K315 to about S323, about P328 to about F336, about A341 to about Q349, about F387 to about Q395, about S403 to about C411, about T409 to about P417, about F443 to about N451, about W451 to about Y459, about A462 to about M470, about G478 to about M486, about A487 to about A495, about V517 to about V525, about T527 to about Q535, about I541 to about F549, about A561 to about V569, about E594 to about C602, about I611 to about H619, about G643 to about I650, about P686 to about K694, about C704 to about S712, about R722 to about I730, about E727 to about T735, about P746 to about G754, about D776 to about L784, about Y799 to about S807, about C808 to about I816, about V818 to about V826, about T835 to about G843, about R883 to about G891, about K932 to about K940, about Q935 to about K943, about T949 to about A957, about S977 to about S985, about S981 to about P989, and about N986 to about L994 of SEQ ID NO:40 (Figures 7A-~~D~~E) correspond to the highly antigenic regions of the TR13 protein, predicted using the Jameson-Wolf antigenic index (See Figure 9 and Table III). These highly antigenic fragments correspond to the amino acid residues illustrated in Figure 7A-~~D~~E and in SEQ ID NO:40. As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the TR13 receptor protein. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0292] Polypeptide fragments of the present invention include polypeptides comprising or alternatively, consisting of, an amino acid sequence contained preferably in

SEQ ID NO:61 or, alternatively, in SEQ ID NO:5, encoded by the cDNA contained in the clone deposited as ATCC Deposit No. PTA-348, or encoded by a nucleic acid which hybridizes (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone, or shown preferably in Figures 10A-H (SEQ ID NO:61) or, alternatively, in Figures 4A-~~D~~E (SEQ ID NO:4) or the complementary strand thereto, or polynucleotide fragments thereof (e.g., as disclosed herein). Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Preferred representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise, or alternatively consist of, from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 231 of SEQ ID NO:61. Alternative, less preferred representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise, or alternatively consist of, from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 226 of SEQ ID NO:5, and the corresponding amino acid residues of SEQ ID NO:61 (as the sequence of amino acid residues T-78 to M-231 of SEQ ID NO:61 is identical to the sequence of amino acid residues T-73 to M-226 of SEQ ID NO:5). Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0295] In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively consist of, one or more TR14 domains. Preferred polypeptide fragments of the present invention include a member selected from the group: (a) a polypeptide comprising or alternatively, consisting of, the TR14 extracellular domain (predicted to constitute preferably amino acid residues from about 1 to about 138 in Figures 10A-H and SEQ ID NO:61, or, alternatively, from about 1 to about 133 of SEQ ID NO:5 and Figures 4A-~~D~~E, or from about 1 to about 133 of SEQ ID NO:5); (b) a polypeptide comprising or alternatively, consisting of, the TR14 cysteine rich domain (predicted to constitute preferably amino acids Cys-31 to Cys-104 of SEQ ID NO:61, or, alternatively, amino acid residues from about 65 to about 88 of Figures 4A-~~D~~E, or from about 65 to about 85 in SEQ ID NO:5); (c) a polypeptide comprising or alternatively,

consisting of, the TR14 transmembrane domain (predicted to constitute amino acid residues from about 139 to about 155 of Figures 10A-H and SEQ ID NO:61 or from about 134 to about 150 of Figures 4A-~~D~~E and SEQ ID NO:5); (d) a polypeptide comprising or alternatively, consisting of, the TR14 intracellular domain (predicted to constitute amino acid residues from about 155 to about 231 of Figures 10A-H and SEQ ID NO:61 or amino acid residues from about 151 to about 226 of Figures 4A-~~D~~E and SEQ ID NO:5); (e) a polypeptide comprising, or alternatively, consisting of, one, two, three, four or more, epitope bearing portions of the TR14 polypeptide (predicted to constitute preferably Asp-2 to Asp-10, Thr-17 to Asp-38, Pro-45 to Ser-52, Pro-88 to Arg-95, Thr-108 to Glu-115, Thr-131 to Glu-136, Phe-166 to Gly-174, Ala-180 to Ala-200, and Gln-224 to Met-231 of SEQ ID NO:61, or the corresponding amino acid sequences in SEQ ID NO:5, as the sequence of amino acid residues T-78 to M-231 of SEQ ID NO:61 is identical to the sequence of amino acid residues T-73 to M-226 of SEQ ID NO:5. Additional epitope bearing TR14 polypeptides comprise or, alternatively, consist of amino acid residues from about 2 to about 24, 42 to about 52, 80 to about 115, and 155 to about 226 of SEQ ID NO:5 (or the corresponding amino acid sequences in SEQ ID NO:61, as the sequence of amino acid residues T-78 to M-231 of SEQ ID NO:61 is identical to the sequence of amino acid residues T-73 to M-226 of SEQ ID NO:5); and (f) any combination of polypeptides (a)-(e). In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0297] Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of TR14 (preferably SEQ ID NO:61 or, alternatively, SEQ ID NO:5). Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of complete (i.e., full-length) TR14 (preferably SEQ ID NO:61 or, alternatively, SEQ ID NO:5). Certain preferred regions are those set out in

Figure 6 and Table II and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted preferably Figures 10A-H (SEQ ID NO:61) or, alternatively, in Figures 4A-~~D~~E (SEQ ID NO:5), such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle predicted hydrophilic and Hopp-Woods predicted hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0299] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the TR14 amino acid sequence shown depicted preferably Figures 10A-H (SEQ ID NO:61) or, alternatively, in Figures 4A-~~D~~E (SEQ ID NO:5), up to the methionine residue at position number 231 of SEQ ID NO:61 (or, number 226 of SEQ ID NO:5) and polynucleotides encoding such polypeptides. In particular preferred embodiments for TR14, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-231 of Figures 10A-H, where n^1 is an integer from 1 to 231 corresponding to the position of the amino acid residue in Figures 10A-H. In alternative embodiments, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-226 of Figures 4A-~~D~~E, where n^1 is an integer from 1 to 226 corresponding to the position of the amino acid residue in Figures 4A-~~D~~E.

[0301] In additional embodiments, N-terminal deletions of the TR14 polypeptides of the invention can be described by the general formula n^2-226, where n^2 is a number from 2 to 221, corresponding to the position of amino acid identified in Figures 4A-~~D~~E (SEQ ID NO:5). N-terminal deletions of the TR14 polypeptide of the invention shown as SEQ ID NO:5 include polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: S-2 to M-226; T-3 to M-226; G-4 to M-226; T-5 to M-226; N-6 to M-226; G-7 to M-226; D-8 to M-226; G-9 to M-226; V-10 to M-226; S-11 to M-226; P-12 to M-226; A-13 to M-226; N-14 to M-226; G-15 to M-226; V-16 to M-226; V-17 to M-226; L-18 to M-226; D-19 to M-226; R-20 to M-226; S-21 to M-226; Y-22 to M-226; P-23 to M-226; R-24 to M-226; I-25 to M-226; V-26 to M-226; V-27 to M-226; M-28 to M-

226; E-29 to M-226; R-30 to M-226; V-31 to M-226; E-32 to M-226; M-33 to M-226; P-34 to M-226; T-35 to M-226; A-36 to M-226; Q-37 to M-226; P-38 to M-226; A-39 to M-226; L-40 to M-226; L-41 to M-226; A-42 to M-226; V-43 to M-226; Q-44 to M-226; K-45 to M-226; Q-46 to M-226; L-47 to M-226; G-48 to M-226; P-49 to M-226; P-50 to M-226; Q-51 to M-226; M-52 to M-226; C-53 to M-226; R-54 to M-226; V-55 to M-226; A-56 to M-226; C-57 to M-226; T-58 to M-226; C-59 to M-226; A-60 to M-226; V-61 to M-226; I-62 to M-226; N-63 to M-226; R-64 to M-226; V-65 to M-226; Q-66 to M-226; K-67 to M-226; V-68 to M-226; N-69 to M-226; C-70 to M-226; T-71 to M-226; P-72 to M-226; T-73 to M-226; S-74 to M-226; N-75 to M-226; A-76 to M-226; V-77 to M-226; C-78 to M-226; G-79 to M-226; D-80 to M-226; C-81 to M-226; L-82 to M-226; P-83 to M-226; R-84 to M-226; F-85 to M-226; Y-86 to M-226; R-87 to M-226; K-88 to M-226; T-89 to M-226; R-90 to M-226; I-91 to M-226; G-92 to M-226; G-93 to M-226; L-94 to M-226; Q-95 to M-226; D-96 to M-226; Q-97 to M-226; E-98 to M-226; C-99 to M-226; I-100 to M-226; P-101 to M-226; C-102 to M-226; T-103 to M-226; K-104 to M-226; Q-105 to M-226; T-106 to M-226; P-107 to M-226; T-108 to M-226; S-109 to M-226; E-110 to M-226; V-111 to M-226; Q-112 to M-226; C-113 to M-226; A-114 to M-226; F-115 to M-226; Q-116 to M-226; L-117 to M-226; S-118 to M-226; L-119 to M-226; V-120 to M-226; E-121 to M-226; A-122 to M-226; D-123 to M-226; A-124 to M-226; P-125 to M-226; T-126 to M-226; V-127 to M-226; P-128 to M-226; P-129 to M-226; Q-130 to M-226; E-131 to M-226; A-132 to M-226; T-133 to M-226; L-134 to M-226; V-135 to M-226; A-136 to M-226; L-137 to M-226; V-138 to M-226; S-139 to M-226; S-140 to M-226; L-141 to M-226; L-142 to M-226; V-143 to M-226; V-144 to M-226; F-145 to M-226; T-146 to M-226; L-147 to M-226; A-148 to M-226; F-149 to M-226; L-150 to M-226; G-151 to M-226; L-152 to M-226; F-153 to M-226; F-154 to M-226; L-155 to M-226; Y-156 to M-226; C-157 to M-226; K-158 to M-226; Q-159 to M-226; F-160 to M-226; F-161 to M-226; N-162 to M-226; R-163 to M-226; H-164 to M-226; C-165 to M-226; Q-166 to M-226; R-167 to M-226; G-168 to M-226; G-169 to M-226; L-170 to M-226; L-171 to M-226; Q-172 to M-226; F-173 to M-226; E-174 to M-226; A-175 to M-226; D-176 to M-226; K-177 to M-226; T-178 to M-226; A-179 to M-226; K-180 to M-226; E-181 to M-226; E-182 to M-226; S-183 to M-226; L-184 to M-226; F-185 to M-226; P-186 to M-226; V-187 to M-226; P-188 to M-226; P-189 to M-226; S-190 to M-226; K-191 to M-226; E-192 to M-226; T-193 to M-226; S-194 to M-226; A-195 to M-

226; E-196 to M-226; S-197 to M-226; Q-198 to M-226; V-199 to M-226; S-200 to M-226; W-201 to M-226; A-202 to M-226; P-203 to M-226; G-204 to M-226; S-205 to M-226; L-206 to M-226; A-207 to M-226; Q-208 to M-226; L-209 to M-226; F-210 to M-226; S-211 to M-226; L-212 to M-226; D-213 to M-226; S-214 to M-226; V-215 to M-226; P-216 to M-226; I-217 to M-226; P-218 to M-226; Q-219 to M-226; Q-220 to M-226; Q-221 to M-226; of SEQ ID NO:5. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0302] In another embodiment, N-terminal deletions of the extracellular domain of the TR14 polypeptide can be described by the general formula n^2-133, where n^2 is a number from 1 to 128, corresponding to the position of amino acids identified in Figures 4A-~~D~~E. N-terminal deletions of the extracellular domain of the TR14 polypeptide of the invention shown as SEQ ID NO:7 include polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: S-2 to T-133; T-3 to T-133; G-4 to T-133; T-5 to T-133; N-6 to T-133; G-7 to T-133; D-8 to T-133; G-9 to T-133; V-10 to T-133; S-11 to T-133; P-12 to T-133; A-13 to T-133; N-14 to T-133; G-15 to T-133; V-16 to T-133; V-17 to T-133; L-18 to T-133; D-19 to T-133; R-20 to T-133; S-21 to T-133; Y-22 to T-133; P-23 to T-133; R-24 to T-133; I-25 to T-133; V-26 to T-133; V-27 to T-133; M-28 to T-133; E-29 to T-133; R-30 to T-133; V-31 to T-133; E-32 to T-133; M-33 to T-133; P-34 to T-133; T-35 to T-133; A-36 to T-133; Q-37 to T-133; P-38 to T-133; A-39 to T-133; L-40 to T-133; L-41 to T-133; A-42 to T-133; V-43 to T-133; Q-44 to T-133; K-45 to T-133; Q-46 to T-133; L-47 to T-133; G-48 to T-133; P-49 to T-133; P-50 to T-133; Q-51 to T-133; M-52 to T-133; C-53 to T-133; R-54 to T-133; V-55 to T-133; A-56 to T-133; C-57 to T-133; T-58 to T-133; C-59 to T-133; A-60 to T-133; V-61 to T-133; I-62 to T-133; N-63 to T-133; R-64 to T-133; V-65 to T-133; Q-66 to T-133; K-67 to T-133; V-68 to T-133; N-69 to T-133; C-70 to T-133; T-71 to T-133; P-72 to T-133; T-73 to T-133; S-74 to T-133; N-75 to T-133; A-76 to T-133; V-77 to T-133; C-78 to T-133; G-79 to T-133; D-80 to T-133; C-81 to T-133; L-82 to T-133; P-83 to T-133; R-84 to T-133; F-85 to T-133; Y-86 to T-133; R-87 to T-133; K-88 to T-133; T-89 to T-133; R-90 to T-133; I-91 to T-133; G-92 to T-133; G-93 to T-133; L-94 to T-133; Q-95 to T-133; D-96 to T-133; Q-97 to T-133; E-98 to T-133; C-99 to T-133; I-100 to T-133; P-101 to T-133; C-102 to T-133; T-103 to T-133; K-104 to T-133; Q-105 to T-133; T-106 to T-133; P-107 to T-133; T-108 to T-133; S-109 to T-133; E-110 to T-133; V-111 to T-133; Q-112 to T-133; C-113

to T-133; A-114 to T-133; F-115 to T-133; Q-116 to T-133; L-117 to T-133; S-118 to T-133; L-119 to T-133; V-120 to T-133; E-121 to T-133; A-122 to T-133; D-123 to T-133; A-124 to T-133; P-125 to T-133; T-126 to T-133; V-127 to T-133; P-128 to T-133; of SEQ ID NO:7 (or the corresponding amino acid sequences in SEQ ID NO:61, as the sequence of amino acid residues T-78 to T-138 of SEQ ID NO:61 is identical to the sequence of amino acid residues T-73 to T-133 of SEQ ID NO:7). Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0306] Alternatively, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the TR14 polypeptide shown in Figures 4A-~~D~~E (SEQ ID NO:5), up to the asparagine residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m^1 of Figures 4A-~~D~~E, where m^1 is an integer from 6 to 226 corresponding to the position of the amino acid residue in Figures 4A-~~D~~E (which is identical to the sequence shown as SEQ ID NO:5).

[0309] The present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the TR14 polypeptide shown in Figures 4A-~~D~~E (SEQ ID NO:5) and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 133-m^1 of Figures 4A-~~D~~E, where m^1 is an integer from 6 to 132 corresponding to the position of the amino acid residue in Figures 4A-~~D~~E (which is identical to the sequence shown as SEQ ID NO:5).

[0318] In additional embodiments, the number of substitutions, additions or deletions in the amino acid sequence of Figures 4A-~~D~~E (SEQ ID NO:5) and/or any of the polypeptide fragments described herein (e.g., the cysteine-rich domain, the extracellular domain, or intracellular domain) is 75, 70, 60, 50, 40, 35, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 30-20, 20-15, 20-10, 15-10, 10-1, 5-10, 1-5, 1-3 or 1-2.

[0323] The polypeptides of the present invention include a polypeptide comprising, or alternatively, consisting of the polypeptide encoded by the cDNA deposited as ATCC Deposit No. PTA-348; a polypeptide comprising, or alternatively, consisting of amino acids from 1 to about 231 of SEQ ID NO:61 or from 1 to about 226 of SEQ ID NO:5; a polypeptide comprising, or alternatively, consisting of amino acids from about

from 2 to about 231 of SEQ ID NO:61 or 2 to about 226 of SEQ ID NO:5; a polypeptide comprising, or alternatively, consisting of amino acids from ~~from~~ 1 to about 138 of SEQ ID NO:61 or from 1 to about 133 of SEQ ID NO:5; a polypeptide comprising, or alternatively, consisting of the extracellular domain of the polypeptide encoded by the cDNA deposited as ATCC Deposit No. PTA-348; a polypeptide comprising, or alternatively, consisting of the cysteine rich domain of the polypeptide encoded by the cDNA deposited as ATCC Deposit No. PTA-348, or as shown in amino acids about 31 to about 104 of SEQ ID NO:61, or shown in amino acids from about 65 to about 85 of SEQ ID NO:5; a polypeptide comprising, or alternatively, consisting of the transmembrane domain of the polypeptide encoded by the cDNA deposited as ATCC Deposit No. PTA-348 (predicted to constitute amino acids from about 139 to about 155 of SEQ ID NO:61 or from 134 to about 150 of SEQ ID NO:5); a polypeptide comprising, or alternatively, consisting of the intracellular domain (predicted to constitute amino acids from about 155 to about 231 of SEQ ID NO:61 or from about 151 to about 226 of SEQ ID NO:5); a polypeptide comprising, or alternatively, consisting of the extracellular and intracellular domains with all or part of the transmembrane domain deleted; as well as polypeptides which are at least 80% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98%, or 99% identical to the polypeptides described above (e.g., the polypeptide encoded by the cDNA in ATCC Deposit No. PTA-348, the polypeptide of Figures 10A-H (SEQ ID NO:61); or the polypeptide of Figures 4A-~~D~~E (SEQ ID NO:5)) or polypeptide fragments thereof, such as those disclosed herein), and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0333] Additional non-limiting examples of predicted antigenic polypeptides that can be used to generate TR14-specific antibodies include: a polypeptide comprising, or alternatively consisting of amino acid residues from about 2 to about 24 in Figures 4A-~~D~~E (corresponding to about amino acid 2 to about 24 in SEQ ID NO:5); a polypeptide comprising amino acid residues from about 42 to about 52 in Figures 4A-~~D~~E (corresponding to about amino acid 42 to about 52 in SEQ ID NO:5); a polypeptide

comprising amino acid residues from about 80 to about 115 in Figures 4A-~~D~~E (corresponding to about amino acid 80 to about 115 in SEQ ID NO:5); and a polypeptide comprising amino acid residues from about 155 to about 226 in Figures 4A-~~D~~E (corresponding to about amino acid 155 to about 226 in SEQ ID NO:5), and the corresponding amino acid sequences of SEQ ID NO:61, as the sequence of amino acid residues T-78 to M-231 of SEQ ID NO:61 is identical to the sequence of amino acid residues T-73 to M-226 of SEQ ID NO:5. As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the TR14 receptor protein. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0334] Additional non-limiting examples of predicted antigenic polypeptides that can be used to generate TR14-specific antibodies include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about T3 to about S11, from about V16 to about R24, from about Q44 to about M52, from about F85 to about G93, from about T103 to about V111, from about F161 to about G169, from about V187 to about A195, from about P218 to about M226 of SEQ ID NO:5 (Figures 4A-~~D~~E, and the corresponding amino acid sequences of SEQ ID NO:61, as the sequence of amino acid residues T-78 to M-231 of SEQ ID NO:61 is identical to the sequence of amino acid residues T-73 to M-226 of SEQ ID NO:5) correspond to the highly antigenic regions of the TR14 protein, predicted using the Jameson-Wolf antigenic index (See Figure 6 and Table II). These highly antigenic fragments correspond to the amino acid residues illustrated in Figure 4A-~~D~~E and in SEQ ID NO:5. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0710] Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature 372*:333-335 (1994). Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding

regions of the TR13 shown in Figures 1A-~~C~~D or Figures 7A-~~D~~E could be used in an antisense approach to inhibit translation of endogenous TR13 mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. While antisense nucleotides complementary to the TR13 coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

[0715] Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature 372*:333-335 (1994). Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of the TR14 shown in Figures 4A-~~D~~E could be used in an antisense approach to inhibit translation of endogenous TR14 mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. While antisense nucleotides complementary to the TR14 coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

[0723] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, Sarver *et al, Science 247*:1222-1225 (1990). While ribozymes that cleave mRNA at site-specific recognition sequences can be used to destroy TR13 mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, *Nature 334*:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of TR13 in Figures 1A-~~C~~D (SEQ ID NO:1) or Figures 7A-~~D~~E (SEQ ID NO:39). Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the TR13 mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[0725] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, Sarver *et al, Science 247*:1222-1225 (1990). While ribozymes that cleave mRNA at site-specific recognition sequences can be used to destroy TR14 mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, *Nature 334*:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of TR14 (preferably Figures 10A-H (SEQ ID NO:60) or, alternatively, Figures 4A-~~D~~E (SEQ ID NO:4)). Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the TR14 mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[0731] In other embodiments, antagonists according to the present invention include soluble forms of TR13 (e.g., fragments of the TR13 shown in Figures 1A-~~C~~D (SEQ ID NO:2) or Figures 7A-~~D~~E (SEQ ID NO:39)) that include the ligand binding domain and/or any combination of one, two, three, four or more of the cysteine-rich domains from the extracellular region of the full-length receptor disclosed in the figures). Such soluble forms of the TR13, which may be naturally occurring or synthetic, antagonize TR13 mediated signaling by competing with the cell surface bound forms of the receptor for binding to TNF-family ligands. Antagonists of the present invention also include antibodies specific for TNF-family ligands, antibodies specific for TR13 polypeptides and TR13-Fc fusion proteins.

[0732] In other embodiments, antagonists according to the present invention include soluble forms of TR14 (e.g., fragments of the TR14 shown preferably in Figures 10A-H (SEQ ID NO:61) or, alternatively in Figures 4A-~~D~~E (SEQ ID NO:5) that include the ligand binding domain, and/or the cysteine-rich domain from the extracellular region of the full-length receptor). Such soluble forms of the TR14, which may be naturally occurring or synthetic, antagonize TR14 mediated signaling by competing with the cell surface bound forms of the receptor for binding to TNF-family ligands. Antagonists of the

present invention also include antibodies specific for TNF-family ligands, antibodies specific for TR14 polypeptides, and TR14-Fc fusion proteins.

[0735] Antibodies according to the present invention may be prepared by any of a variety of methods using TR13 immunogens and/or antigens of the present invention. As indicated, such TR13 immunogens and/or antigens include the full-length TR13 polypeptide and TR13 polypeptide fragments such as, the extracellular domain, any one of the four cysteine rich domains disclosed in Figures 1A-~~C~~D and/or Figures 7A-~~D~~E, the ligand binding domain, or any combination thereof.

[0740] Antagonists according to the present invention include soluble forms of TR13, i.e., TR13 fragments that include the ligand binding domain, and/or any combination of one, two, three, four or more of the cysteine-rich domains from the extracellular region of the TR13 polypeptide sequence shown in Figures 1A-~~C~~D or Figures 7A-~~D~~E. Such soluble forms of the receptor, which may be naturally occurring or synthetic, antagonize TR13 mediated signaling by competing with the cell surface TR13 for binding to TNF-family ligands (See, for example, Examples 34 and 35). Additionally, soluble TR13 may bind to apoptosis inducing TNF ligands such as TRAIL, FasL, or AIM-II and more effectively compete for TRAIL, FasL, AIM-II, binding, or other TNF family member, reducing the available TRAIL, FasL, AIM-II, or other TNF family member, for binding to receptors with functional death domains. Thus, soluble forms of the receptor that include the ligand binding domain and/or one or more cysteine rich domains of TR13 are novel cytokines capable of inhibiting apoptosis induced by TNF-family ligands (See, for example, Examples 34 and 35). These are preferably expressed as dimers or trimers, since these have been shown to be superior to monomeric forms of soluble receptor as antagonists, e.g., IgGFc-TNF receptor family fusions. Other such cytokines are known in the art and include Fas B (a soluble form of the mouse Fas receptor) that acts physiologically to limit apoptosis induced by Fas ligand (D.P. Hughes and I.N. Crispe, *J. Exp. Med. 182*:1395-1401 (1995)).

[0794] 5'-CGCCCATGGATGGACCAAAGTACC-3' (SEQ ID NO: 23) containing the underlined NcoI restriction site followed by nucleotides complementary to the amino terminal coding sequence of the mature TR13 sequence in Figures 1A-~~C~~D, respectively. One of ordinary skill in the art would appreciate, of course, that the point in the protein

coding sequence where the 5' primer begins may be varied to amplify a desired portion of the complete protein shorter or longer than the described form.

[0796] 5'-CGCCCATGGATGAGTACTGGGACC-3' (SEQ ID NO: 24) containing the underlined NcoI restriction site followed by nucleotides complementary to the amino terminal coding sequence of the mature TR14 sequence in Figures 4A-~~D~~E, respectively. One of ordinary skill in the art would appreciate, of course, that the point in the protein coding sequence where the 5' primer begins may be varied to amplify a desired portion of the complete protein shorter or longer than the described form.

[0798] 5'- GCAGCACATATGATGGCTGAGCCTGGGCAC -3' (SEQ ID NO: 42) containing the underlined NdeII restriction site followed by nucleotides complementary to the amino terminal coding sequence of the mature TR13 sequence in Figures 7A-~~D~~E, respectively. One of ordinary skill in the art would appreciate, of course, that the point in the protein coding sequence where the 5' primer begins may be varied to amplify a desired portion of the complete protein shorter or longer than the described form.

[0800] 5'- GCAGCATCTAGAGCGGCACTGAGTCAAATCCATC -3' (SEQ ID NO:25) containing the underlined HindIII site followed by nucleotides complementary to the 3' end of the non-coding sequence in the TR13 sequence in Figure 1A-~~C~~D.

[0802] 5'-CGCAAGCTTCATTCAGGCCCCTGCTG-3' (SEQ ID NO:26) containing the underlined HindIII site followed by nucleotides complementary to the 3' end of the non-coding sequence in the TR14 DNA sequence in Figures 4A-~~D~~E.

[0804] 5'- GCAGCATCTAGAGCGGCAGTGAGTCAAATCCATC -3' (SEQ ID NO:43) containing the underlined HindIII site followed by nucleotides complementary to the 3' end of the non-coding sequence in the TR13 DNA sequence in Figures 7A-~~D~~E.

[0814] The cDNA sequence encoding the TR13 and/or TR14 receptor protein in the deposited clone (s), lacking the AUG initiation codon and the naturally associated leader sequence shown in Figures 1A-~~C~~D (SEQ ID NO:2), Figures 7A-~~D~~E (SEQ ID NO:40), and Figures 4A-~~D~~E (SEQ ID NO:5), and respectively, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene.

[0815] The 5' TR13 primer has the sequence 5' CGCGGATCCATGGATGGACCAA AGTACC 3' (SEQ ID NO:27) containing the underlined BamHI restriction enzyme site, an efficient signal for initiation of translation

in eukaryotic cells, as described by M. Kozak, *J. Mol. Biol. 196*:947- 950 (1987), followed by bases of the sequence of the mature TR13 protein shown in Figures 1A-~~C~~D, beginning with the indicated N-terminus of the mature protein.

[0816] The 5' TR14 primer has the sequence 5' CGCGGATCCATGGATGAGTACTG GGACC 3' (SEQ ID NO:28) containing the underlined BamHI restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells, as described by M. Kozak, *J. Mol. Biol. 196*:947- 950 (1987), followed by bases of the sequence of the TR14 polypeptide shown in Figures 4A-~~D~~E, respectively, beginning with the indicated N-terminus of the mature protein.

[0817] The 5' TR13 primer has the sequence 5' GCAGCATCTAGACCGCCATC ATGGCTGAGCCTGGGCACAGCCACCATC 3' (SEQ ID NO:44) containing the underlined XbaI restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells, as described by M. Kozak, *J. Mol. Biol. 196*:947- 950 (1987), followed by bases of the sequence of the TR13 polypeptide shown in Figures 7A-~~D~~E, respectively, beginning with the indicated N-terminus of the mature protein.

[0818] The 3' primer for TR13 has the sequence 5' CGCGGTACCGCGGCACTGAG TCAAATC 3' (SEQ ID NO:29) containing the underlined Asp718 restriction site followed by nucleotides complementary to the 3' noncoding sequence in Figures 1A-~~C~~D.

[0819] The 3' primer for TR14 has the sequence 5' CGCGGTACCCATTCAGGCCCC TGCTG 3' (SEQ ID NO:30) containing the underlined Asp718 restriction site followed by nucleotides complementary to the 3' noncoding sequence in Figures 4A-~~D~~E, respectively.

[0820] The 3' primer for TR13 has the sequence 5' GCAGCATCTAGAGCGGCACT GAGTCAAATC 3' (SEQ ID NO:45) containing the underlined XbaI restriction site followed by nucleotides complementary to the 3' noncoding sequence in Figures 7A-~~D~~E, respectively.

[0840] The 5' TR13 primer of the sequence described in Figures 7A-~~D~~E (SEQ ID NO:39), 5' CGCGGATCCATGGCTGAGCCTGGGCAC 3' (SEQ ID NO:46) contains the underlined BamHI site, an ATG start codon and 5 codons thereafter. The 3' primer for TR, which contains the underlined XbaI site, stop codon, hemagglutinin tag, and the last 18 nucleotides of the 3' coding sequence (at the 3' end), has the following sequence: 5'

CGCTCTAGATCAAGCGTAGTCTGGGACGTCGTATGGGTAGCGGCACTGAGTCA
AATC 3' (SEQ ID NO:47).